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(54) Title: FORMULATION AND METHOD FOR TREATING CONGESTIVE HEART FAILURE

(57) Abstract

This invention provides a method for treating congestive heart failure comprising administering an effective amount of 4-chloro-5-(imidazoline-2-ylamino)-6-methoxy-2-methylpyrimidine in an oral or implant nonimmediate release formulation and nonimmediate release formulations.

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Title

FORMULATION AND METHOD FOR TREATING CONGESTIVE HEART FAILURE

Cross Reference

This application is a continuation-in-part of application Serial No. 08/659,463, filed June 6, 1996.

Field Of The Invention

The present invention is in the fields of pharmacology and pharmaceutical chemistry and provides formulations and a method for using 4-chloro-5-(imidazoline-2-ylamino)-6-methoxy-2-methylpyrimidine for the treatment of congestive heart failure.

Background Of The Invention

Congestive heart failure (CHF) may be defined as an inability of the heart to supply the metabolic demands of the periphery with sufficient blood for proper nutrition and waste removal. The term describes a complicated symptom complex which may include dyspnea, fatigue, pulmonary congestion, an enlarged heart and peripheral edema. CHF is the end result of long-term or severe cardiac or circulatory deficits. It is often caused by long-standing hypertension, acute myocardial infarction, valvular disease, idiopathic cardiomyopathy and a wide variety of secondary insults. CHF incidence is increasing and is the most frequent cause of hospitalization in patients over 65 years of age.

Early in the syndrome, both cardiac and peripheral regulatory mechanisms come into play to help counteract the primary failure of the pump. For instance, the heart rate increases, left ventricular volume and pressure may rise and the heart may dilate and/or undergo hypertrophy (currently termed a remodeling process). In the periphery, blood volume is increased, sodium and water are retained and a reflex increase in the activity of the sympathetic nervous system enhances arterial and venous tone and increases

contractility of the heart. Primarily as a result of the increased activity of the sympathetic nervous system, a panoply of neurohormones are elevated in the plasma including: norepinephrine, renin, neuropeptide Y (NPY), angiotensin II, aldosterone, vasopressin and atrial natriuretic factor. These compensatory changes act together to maintain perfusion of vital beds such as the brain and heart. Although these potent mechanisms may have evolved originally to protect against acute loss of blood volume (e.g. hemorrhage), in the state of chronic CHF, continued activation of compensatory mechanisms (especially the sympathetic system) may act to impede efficient cardiac function by making it more difficult for the heart to eject blood. Moreover, the inappropriate elevation of peripheral neurohormones contributes to the exacerbation of many of the symptoms of CHF such as pulmonary and peripheral edema, dilutional hyponatremia and hypokalemia.

The activation of neurohormonal systems in particular can contribute to the maintenance of a positive feedback loop that can perpetuate the cycle leading to a further decline in the status of the patient. For instance, increased sympathetic tone may lead directly to an increase in cardiac rate, myocyte necrosis and hypertrophy leading to increased myocardial remodeling, increased wall tension and diastolic dysfunction resulting in increased heart failure. Increased activity of the sympathetic nervous system also stimulates epinephrine, norepinephrine and renin release which in turn increase further the impedance to ventricular ejection and decreases blood flow to the kidneys. The latter acts as a further stimulus for activation of the renin-angiotensin system, and the cycle is perpetuated. Clinically, it is now well-appreciated that patients with CHF have increased sympathetic activation and elevations in plasma concentration of norepinephrine and renin, and that excessive elevations of neurohormones are an important prognostic factor.

The complexity of the syndrome has allowed numerous pharmacological interventions to be explored. These range from drugs that stimulate the heart directly, such as digitalis, β-agonists and phosphodiesterase inhibitors to compounds that directly relax the peripheral vasculature such as nitrates, certain calcium channel blockers, α-blockers and directly acting vasodilators, such as hydralazine. However, the best results to date in treating CHF have been achieved with agents that in some way act to interrupt the positive feedback cycle referred to above. Inhibition of excessive neurohormonal activation seems to be particularly beneficial. Thus, ACE inhibitors have been useful adjuncts to therapy and are now recommended for almost all patients with this disorder. Recent trials of β-blockers are especially intriguing since it was long thought that directly interfering with the compensatory function of the sympathetic nervous system to stimulate contractility and maintain blood pressure might worsen CHF. In fact, judicious use of such agents has proven beneficial especially in cardiomyopathy as opposed to ischemic heart disease. Moreover, certain β-blockers such as bucindolol and carvedilol may also decrease plasma renin and norepinephrine. Even so, the best drug therapy paradigm has improved survival only about 10-15% and overall morbidity and mortality in CHF remains dismal. In fact, norepinephrine turnover in the CNS and periphery in New York Heart Association class III and IV CHF patients was still markedly elevated even with optimal digitalis and ACE inhibitor therapy.

Many clinicians are beginning to think of CHF as a neurohormonal disorder. Therefore, an agent acting via the CNS to interrupt sympathetic drive and attendent neurohormonal stimulation to the diseased heart and periphery might favorably influence the morbidity and mortality of patients with CHF. Interestingly, this hypothesis has never been adequately tested. Clonidine was examined in a clinical trial, but only 13 patients were

enrolled and treatment duration was relatively short (12 weeks), Giles et al., Angiology, 38, 537-548, (1987). Nevertheless, favorable trends were reported including reductions in heart rate, increase in ejection fraction and improvement in functional status.

Based on what is now known about the importance of local and systemic activation of the sympathetic nervous system in the pathophysiology of CHF, moxonidine has been suggested as a potentially beneficial therapeutic agent, Mangiapane et al., FASEB, 9, 265 (1995), Michel et al., J. Cardiovasc. Pharmacol., 20, Supp. 4, 524-530, (1992).

Elevated systolic and diastolic blood pressure are major risk factors for cardiovascular disorders such as myocardial infarction, coronary artery disease, and stroke. While it is well-recognized that hypertension is particularly related to the risk of strokes, it is less appreciated that hypertension is also an important risk factor for coronary heart disease; equally important as elevated serum lipids. Hypertension is generally defined as an elevation of systolic and/or diastolic blood pressures to above 140/90 mm Hg and is the most common cardiovascular disease. In the United States alone, about 20-40 million people require treatment for hypertension. The currently available therapies include converting enzyme inhibitors, diuretics, vasodilators, beta blockers, central antisympathetic agents, and Ca++ channel antagonists. Blood pressure is a function of vascular resistance, intravascular volume, cardiac output and the contractile state of the blood vessels. Many physiological systems are involved in regulating the homeostasis of intravascular volume, mainly through renal salt and water excretion. Cardiac output is regulated both by intrinsic cardiac factors and by extrinsic factors and the sympathetic nervous systems. The contractile state of the blood vessels is determined by intrinsic vascular factors, the sympathetic nervous system, relaxing factors from endothelial cells, the renin angiotensin system (RAS) and fluid balance. The RAS is the

principle means by which the body controls fluid, electrolyte balance, and blood pressure. It is part of a complex homeostatis mechanism that involves a variety of hormones, enzymes, and autonomic signals.

The key physiologic end product of the RAS is the octapeptide Angiotensin II. The physiological activation of the RAS may be viewed as a primitive yet highly developed system evolved to protect the organism against sudden loss of blood volume or more gradual loss of sodium. Thus, Angiotensin II increases perfusion pressure of vital beds and promotes readsorption of sodium and water. The latter affects occur through the action of aldolsterone and vasopressin on the kidney.

Overactivity of the local RAS may be responsible for end-organ abnormalities associated with chronic hypertension. For instance, Angiotensin II is known to be an important mediator of smooth muscle cell growth and differentiation. Thus, Angiotensin II may mediate the vascular proliferative response that accompanies injury to the vessel wall by mechanical means (i.e. angioplasty) or long-term elevated systemic pressure. As noted above, Angiotensin II is an important regulator of glomerular function, and overactivity of the RAS is undoubtedly an important factor in the development and progression of renal diseases such as diabetic nephropathy and the hyperfiltration glomerulonephropathies.

The two enzymes, renin and angiotensin converting enzyme (ACE), are primarily responsible for the generation of Angiotensin II and are widely distributed throughout the body. Although renin and prorenin are synthesized in the juxtaglomerular (JG) cells of the kidney and released into the circulation, more recent data suggests strongly a broader distribution. For instance, renin and/or its mRNA are found in the brain, blood vessels, anterior pituitary, adrenal cortex, kidney, ovary, uterus, and heart. Renin is subject to feedback inhibition by Angiotensin II as well as

by elevated glomerular pressures and an increase in the sodium load.

ACE is a dipeptidyl carboxypeptidase found mainly in association with the capillary lining of the lung. Like Renin, it is also widely distributed, being located in blood vessels, heart, kidney, intestinal tract, and liver. ACE mediates the removal of the terminal dipeptide from Angiotensin I and also catalyzes the breakdown of bradykinin. In Angiotensin II synthesis, ACE is not a rate limiting factor. Furthermore, it lacks specificity, requiring only a tripeptide sequence with a free carboxy group (as long as the intermediate amino acid is not proline). Consequently, a variety of endogenous peptides are substrates for the enzyme including enkephalins, substance P and Lys-bradykinin.

Renin release from the juxtaglomerular (JG) cells in the kidney is inhibited by a direct action of Angiotensin II on the JG cells. Angiotensin II also stimulates aldosterone secretion which increases sodium retention and increases potassium excretion in the kidney. With increased sodium retention, intravascular volume increases and thus inhibits renin secretion. These feedback loops are divided into long (volume), short (circulating angiotensin II), and ultra-short (intra-JG cell angiotensin II). Many pharmacological interventions are activators or inactivators of renin secretion. Specifically, many drugs used in high blood pressure treatment directly or indirectly alter renin secretion. This effect may counteract or enhance the effect of the medicine used to treat high blood pressure.

Renin and angiotensinogen are also located in the vessel walls and in the brain. This has been termed as the extra renal renin-angiotensin-system (RAS). Thus, the low renin levels and the non-responsiveness of renin secretion to physiological stimuli in hypertensives may be masked by the presence of a very active extravascular renin system.

Agents which interfere with the renin angiotensin system have been used for over 15 years to treat hypertension.

The clinically and therapeutically more successful Angiotensin converting enzyme (ACE) inhibitors were introduced in the marketplace about 14 years ago and have been a mainstay in the treatment of mild to severe hypertension. These are used either as solo agents or in combination with diuretics (which considering the physiology of the renin angiotensin system is rational). This is because volume and salt depletion tends to increase renin secretion (as volume control), thus inhibition of the angiotensin system would lower the blood pressure even more.

In 1991 moxonidine, a central acting antihypertensive agent, was approved in Germany. Research in receptor-pharmacology showed that moxonidine is a selective agonist at imidazoline$_1$-receptors in the centrolateral medulla.

The use of predominantly alpha$_2$-adrenoceptor-agonists, such as clonidine, although useful, showed a high rate of side effects, such as sedation, dry mouth, and other non-specific effects. These side effects are explained by a stimulation of pre- and postsynaptic alpha$_2$-adrenoceptors within the CNS. Further investigations showed that centrally acting drugs like clonidine and moxonidine develop their antyhypertensive action through binding at imidazoline-receptors, whereas the side-effects are induced by the action at the alpha$_2$-receptors. Differences between moxonidine and clonidine in clinical tolerability are explained by the greater selectivity of moxonidine for imidazoline-receptors rather than alpha$_2$-receptors.

Having been approved in Germany since 1991, there is fairly extensive clinical experience with moxonidine administered in an immediate release formulation. Moxonidine is almost completely absorbed from the gastrointestinal tract (absorption > 90%). Bioavailability is 88%, and the drug does not accumulate with repeated

administration. Simultaneous food intake has no significant effect on absorption or bioavailability of moxonidine. Plasma half life ($t_{1/2}$) is between 2 and 3 hours. Maximum plasma concentration (C_{max}) after intake of 0.2 mg moxonidine is 1 - 3 ng/ml. The maximum plasma level occurs in 30 - 180 minutes. The duration of the antihypertensive effect (up to 24 hours), in contrast to the plasma half life, may be due to moxonidine's slower clearance from its central sites of action (deep compartment). Moxonidine has low plasma protein binding of 7% and is over 60% eliminated unchanged by the renal route. In patients with impaired renal function, peak plasma concentration (C_{max}), plasma half life and area under plasma concentration curve from 0 - 24 hours (AUC_{0-24}) are increased, but no accumulation occurs.

Moxonidine has turned out to be a very well tolerated antihypertensive drug. As a typical side effect, dry mouth occurred in 2 - 15% of patients but usually improved with ongoing treatment. Other side effects like tiredness, headache and dizziness appeared in just a few patients. After acute administration moxonidine lowered plasma levels of norepinephrine and epinephrine, and plasma renin activity was decreased. Moxonidine has no influence on the circadian rhythm of blood pressure. No rebound phenomenon was seen after cessation of treatment. Moxonidine is a well tolerated antihypertensive agent alone and in combination with other antihypertensive drugs, such as diuretics, calcium-antagonists and ACE-inhibitors.

It was demonstrated that moxonidine is a suitable medication for hypertensive drivers. It is neutral in respect to metabolic parameters and causes no respiratory depression, which is important in treatment of antihypertensive asthmatic patients.

In clinical studies 0.2 - 0.4 mg moxonidine has been an effective daily dose range, with reductions in blood pressure between 10 and 20%. The antihypertensive efficacy of moxonidine was confirmed in open studies of up to 2 years

duration as well as in comparative studies of up to 6 months duration.

In one of the earlier studies moxonidine was administered in dose of 0.2 mg once daily or 0.2 mg twice daily, while blood pressure decrease from baseline was 27/19 or 29/15 mmHg respectively. A similar blood pressure reduction of 27/16 mmHg was obtained in 49 patients followed for two years demonstrating that the antihypertensive effect dose does not diminish with time, i.e. tolerance does not develop.

In 141 patients undergoing 12 months' treatment, where dosage was individually titrated to obtain goal diastolic pressure of < 95 mmHg, mean blood pressure fell from 173/103 to 151/88 mmhg. With 0.2 mg moxonidine once daily 82 patients (58.2%) were treated effectively, 53 patients (37.6%) needed 0.2 mg moxonidine twice daily, besides: 1 patient 0.1 mg daily; 4 patients: 0.6 mg daily; 1 patient: 0.8 mg daily. Blood pressure control occurred mostly within three weeks of beginning moxonidine therapy and was consistently maintained throughout the one year study period.

In a surveillance study in 9295 hypertensives, moxonidine was an efficacious and safe antihypertensive agent which improves quality of life. Following a 12 week treatment period, blood pressure decreased and heart rate was slightly reduced by 3 beats/minute. Clinical laboratory parameters remained unchanged except for slight reductions in uric acid, glucose, triglyceride and cholesterol. In 6.9% of patients side effects were reported.

According to the results of the Framingham Heart Study, left ventricular hypertrophy caused by hypertension is the most common reason for CHF with poor prognosis.

Desirably an antihypertensive drug should induce regression of myocardial hypertrophy, which often proceeds heart failure. Some evidence exists that therapeutic regimens, which lead to a decrease in growth-factors, i.e. norepinephrine and angiotensin II, induce regression of left

ventricular hypertrophy. In a smaller study, the antihypertensive effect and regression of left ventricular hypertrophy were evaluated in 20 hypertensive patients. After 6 months therapy with moxonidine, blood pressure was decreased and left ventricular septal thickness was significantly reduced from 22.5 mm to 19.1 mm (mean).

Drugs, especially ACE-inhibitors, used in the treatment of hypertension are increasingly important in the treatment of congestive heart failure. These drugs generally have peripheral sites of action and therefore provoke counter-regulatory effects by way of increased sympathetic activity or stimulation of the renin-angiotensin-aldosterone system.

The self-regulating cardiovascular-system counteracts drug-induced changes with compensatory reflex mechanisms. Centrally acting drugs avoid compensatory counter-regulations, particularly the increase of sympathetic tone, which may play a role in the pathogenesis and maintenance of hypertensive organ-alterations. In view of the increased sympathetic activity in the majority of hypertensive patients and in patients with congestive heart failure, it seems reasonable to control both indications with centrally acting drugs.

Moxonidine reduces systemic vascular resistance while increasing cardiac output in hypertensive patients. These hemodynamic changes may have beneficial effects in patients suffering from symptomatic congestive heart failure.

In a four week open therapy study in patients with essential arterial hypertension or congestive heart failure, patients received 0.2 - 0.4 mg moxonidine daily in the commercially available immediate release formulation as monotherapy or in addition to other medication. Blood pressure and left ventricular ejection fraction were determined at rest and during exercise, after acute administration of 0.1 mg moxonidine and after a four-weeks treatment period. Six patents with CHF were described as

casuistics. In two patients, the ejection fraction worsened. One of them showed poor results after acute drug administration and did not undergo chronic therapy. In two patients the results were basically unchanged. One patient showed clear improvement in acute administration and in chronic treatment as well. Another patient also suffering from arterial hypertension showed just a slight improvement in left ventricular ejection fraction due to moxonidine therapy, but hypertension was well controlled so that the patient continued therapy with 0.2 mg b.i.d. moxonidine. No uniform response to treatment with moxonidine occurred in these patients.

In single dose study moxonidine was administered as the commercially available immediate release formulation to determine the effects on hemodynamics and hormones involved in hemodynamic regulation at rest and during exercise in patients suffering form congestive heart failure.

Ten patients, all suffering from congestive heart failure (NYHA class III) were included in an open study. Moxonidine was administered as a single oral dose of 0.4 mg. Hemodynamic and neurohumoral parameters at rest and during exercise were investigated before as well as 1, 2 and 3 hours after drug intake. Pulmonary pressure indices and cardiac output were determined both at rest and during ergometric exercise by means of Swan-Ganz catheterisation.

There were no clinical relevant alterations in right ventricular and pulmonary pressure indices. Cardiac output and heart rate fell slightly while stroke volume increased. Statistical insignificant reductions in both systemic and pulmonary vascular resistance at rest and during exercise following moxonidine intake were seen. In these normotensive patients blood pressure fell in a time-dependent manner both at rest and at maximum exercise. In regard to neurohumoral effects, a decrease in plasma-renin-activity, both at rest and during maximum exercise, was observed.

Pronounced decreases in norepinephrine plasma levels at rest and during exercise have been seen, whereby only minor reductions in plasma epinephrine were recorded. There were also remarkable decreases in plasma levels of angiotensin II after moxonidine intake. No relevant changes of aldosterone and ANF in plasma were recorded in this single dose trial.

These findings indicate that moxonidine has no detrimental effects on hemodynamic parameters in patients with congestive heart failure. While cardiac output and stroke volume remain virtually unchanged, pressure indices tend to decrease. Following an acute oral administration of moxonidine no neurohumoral counter-regulation has been observed. In evaluation of adverse events and laboratory parameters moxonidine was safe and well tolerated in heart failure patients after a single dose of 0.4 mg.

It has been unexpectedly discovered that administration of the current commercial formulation (immediate release) of 4-chloro-5-(imidazoline-2-ylamino)-6-methoxy-2-methylpyrimidine, moxonidine, produces an unacceptable oscillating reduction in sympathetic activity in CHF patients. A large, but transient, reduction was observed 1-3 hours after dosing. Both the intensity and short duration of the peak effect are undesirable. Clearly, the potential efficacy of moxonidine as a therapeutic agent for congestive heart failure will not be realized unless the peak intensity can be diminished and the duration of action can be extended without engendering the problems inherent in a multiple dosing regimen. It could not have been predicted in light of the cumulative laboratory and clinical experience with moxonidine in hypertension, as well as limited experience in CHF patients, that administration of the present commercial formulation of moxonidine to CHF patients would fail to produce a more sustained reduction in sympathetic activity.

Summary Of The Invention

The presently claimed invention provides a method of treating congestive heart failure comprising administering to a mammal in need of such treatment, an effective dose of moxonidine, or a pharmaceutically acceptable salt thereof, in a nonimmediate release formulation.

The invention also provides pharmaceutical formulations comprising an effective dose of moxonidine, or a pharmaceutically acceptable salt thereof, in association with one or more carriers, diluents or excipients to afford nonimmediate release of said moxonidine.

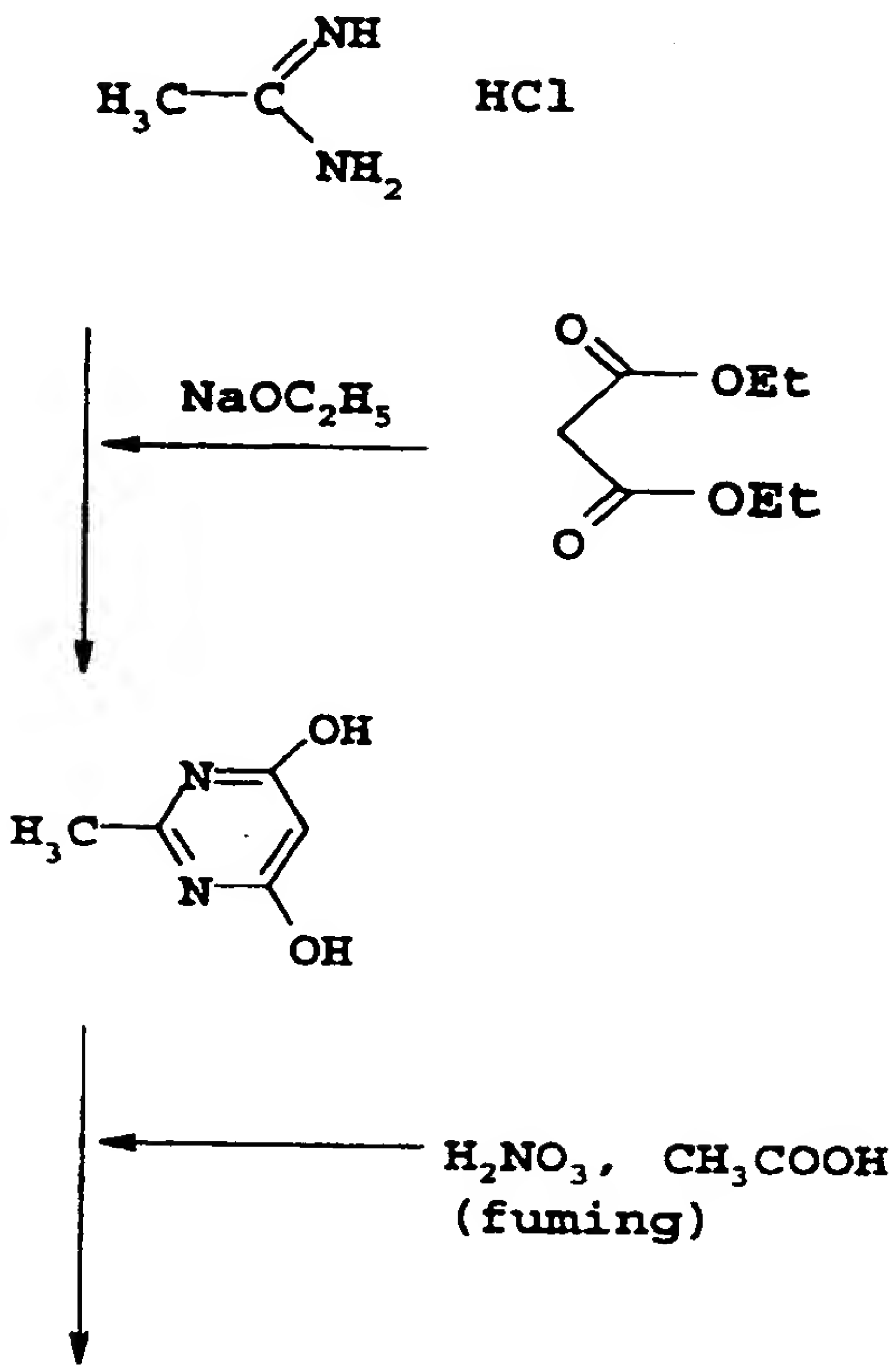
The present invention further provides a method and formulations to afford a mean plasma elimination half-life of from 6 to 16 hours.

Further, the present invention provides a method and formulations to afford a mean time to maximum plasma concentration of from 2.5 to 5 hours.

Detailed Description of the Invention

The compound 4-chloro-5-(imidazoline-2-ylamino)-6-methoxy-2-methylpyrimidine (moxonidine) is known and described in U.S. Patent No. 4,323,570 which is incorporated herein by reference in its entirety.

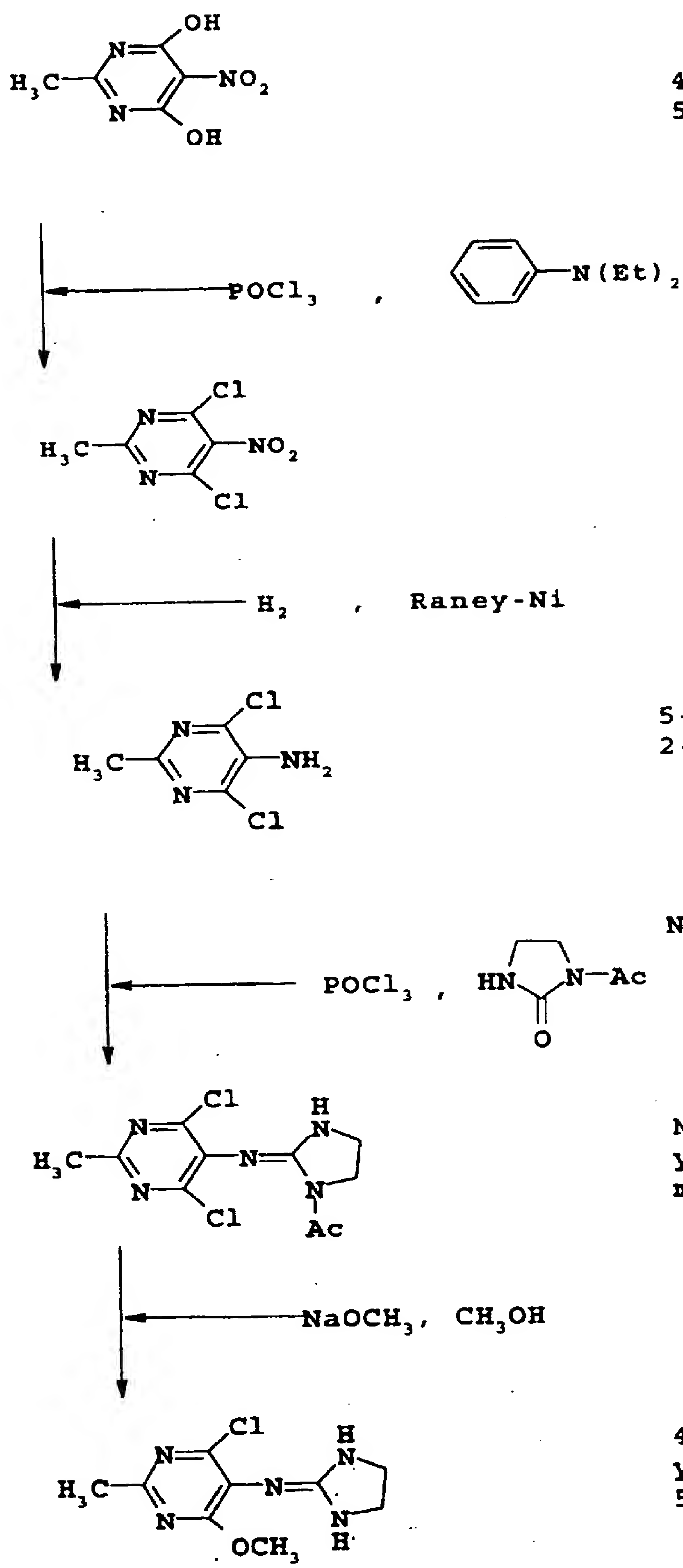
The compound 4-chloro-5-(imidazoline-2-ylamino)-6-methoxy-2-methylpyrimidine is prepared generally as disclosed in U.S. Patent 4,323,570. Preferably, 4-chloro-5-(imidazoline-2-ylamino)-6-methoxy-2-methylpyrimidine is prepared as follows.



Acetamidine hydrochloride

Diethyl malonate

4,6-Dihydroxy-2-methylpyrimidine



4,6-Dihydroxy-2-methyl-5-nitropyrimidine

4,6-Dichloro-2-methyl-5-nitropyrimidine

5-Amino-4,6-dichloro-2-methylpyrimidine

N-Acetylimidazolin-2-one

N-(1-Acetylimidazolin-2-ylidene)-4,6-dichloro-2-methyl-5-pyrimidineamine

4-Chloro-N-(imidazolidin-2-ylidene)-6-methoxy-2-methyl-5-pyrimidinamine

N-acetelimidazoline-2-one is prepared by reacting acetic anhydride with 2-imidazolidone at room temperature. The reaction mixture is heated to between 80 °C and 100 °C for 90 minutes and then cooled to from about 10 °C to about -10 °C to afford N-acetelimidazoline-2-one.

The first intermediate, 4,6-dihydroxy-2-methylpyrimidinamine, is synthesized by preparing sodium ethoxide in situ from sodium and anhydrous ethanol under a nitrogen blanket. Acetamidine hydrochloride and diethyl malonate are added and the reaction mixture heated to boiling for 2 to 5 hours to afford 4,6-dihydroxy-2-methylpyrimidine.

The second intermediate, 4,6-dihydroxy-2-methyl-5-nitropyrimidine, is then synthesized by slowly adding 4,6-dihydroxy-2-methylpyrimidine to a reaction mixture of fuming nitric acid in acetic acid. Once addition of 4, 6-dihydroxy-2-methylpyrimidine is complete, the reaction mixture is stirred for one-half to 2 hours to afford 4,6-dihydroxy-2-methyl-5-nitropyrimidine.

Following the nitration, phosphorous oxychloride ($POCl_3$) and 4,6-dihydroxy-2-methyl-5-nitropyrimidine are combined with stirring. To this mixture, diethylaniline is added dropwise at a rate so that the reaction mixture temperature is maintained below about 40 °C. After the addition is complete, the reaction mixture is refluxed for one to three hours and then distilled under a vacuum to afford the third intermediate, 4,6-dichloro-2-methyl-5-nitropyrimidine.

The third intermediate, 4,6-dichloro-2-methyl-5-nitropyrimidine is hydrogenated over Raney-Ni as a 10% to 30% solution in toluene to afford the corresponding compound, 4,6-dichloro-2-methyl-5-aminopyrimidine, as a fourth intermediate.

The fifth intermediate, N-(1-acetylimidazolin-2-ylidene)-4,6-dichloro-5-pyrimidinamine, is then prepared by combining phosphorous oxychloride, N-acetylimidazolin-2-one and 5-amino-4,6-dichloro-2-methylpyrimidine, and heating to

boiling during from 2 to 4 hours, and then cooling, with stirring to room temperature.

The final product, 4-chloro-N-(imidazolin-2-ylidene)-6-methoxy-2-methyl-5-pyrimidinamine is synthesized by first preparing sodium methoxide in situ from anhydrous methanol and sodium. The fifth intermediate, N-(1-acetylimidazolin-2-ylidene)-4,6-dichloro-2-methyl-5-pyrimidinamine, is added and the reaction mixture brought to a boil. From 15 minutes to 1 hour after the reaction mixture is brought to a boil, further sodium methoxide is added and the reaction mixture is maintained at a boil for from 15 minutes to 1 hour to afford 4-chloro-N-(imidazolin-2-ylidene)-6-methoxy-2-methyl-5-pyrimidinamine.

Work-up of the several intermediates are carried out by standard techniques well-known to those skilled in the art. The various reactants and reagents used in this synthesis are commercially available or readily prepared from commercially available material by standard methods well-known to those skilled in the art.

It will be appreciated that the compound of the present invention may be isolated per se or may be converted to an acid addition salt using conventional methods. As mentioned above, the invention includes pharmaceutically acceptable salts of moxonidine. Moxonidine can react with any of a number of nontoxic inorganic and organic acids, to form a pharmaceutically acceptable salt. Acids commonly employed to form acid addition salts are inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids such as p-toluene-sulfonic, methanesulfonic acid, oxalic acid, p-bromophenyl-sulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like. Examples of such pharmaceutically acceptable salts thus are the sulfate pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate,

acrylate, formate, isobutyrate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, sulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, gamma-hydroxybutyrate, glycollate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate, and the like. Preferred pharmaceutically acceptable acid addition salts are those formed with mineral acids such as hydrochloric acid, hydrobromic acid and sulfuric acid.

By the term "effective dose" is meant an amount of 4-chloro-5-(imidazoline-2-ylamino)-6-methoxy-2-methylpyrimidine, or a pharmaceutically acceptable salt thereof, which will diminish or relieve one or more symptoms or conditions associated with congestive heart failure, hypertension, or both. The term "treating" as used herein includes therapeutic and prophylaxis of the symptoms and named condition and amelioration or elimination of the condition once it has been established. "Plasma elimination half-life" refers to the time required after administration of a single dose to reduce the amount of moxonidine in the plasma by 50 percent. At times, plasma elimination half-life will be referred to herein as $t_{1/2}$. "Time to maximum plasma concentration" refers to the time required after administration of a single dose for moxonidine to reach the maximum concentration in the plasma. Unless otherwise stated, "mean" when associated with plasma elimination half-life and time to maximum plasma concentration refers to the geometric average of stated values. Procedures for determining plasma concentrations of moxonidine are described below.

The compound of the present invention is an I_1-imidazoline ligand demonstrating substantial selectivity for I_1 receptors over α_2 adrenergic receptors. In saturation

binding experiments in bovine rostral ventrolateral medulla (bovine RVLM), moxonidine demonstrates a selectivity value (K_i at α_2 sites in uM/K_i at I_1 sites in uM) of greater than 20 and preferably greater than 30 X, where K_i is the inhibitory affinity constant. Of course, K_i is inversely proportional to affinity, so lower K_i values indicate higher affinity. Thus, the higher the selectivity value, the more selective the compound. In contrast, clonidine's selectivity value in bovine RVLM is less than 4. See Ernsberger et al., J. Pharmacol. Exp. Ther., 264, 172-182 (1993) for details on experimental protocol and results.

As used herein, the term "mammal" means the Mammalia class of higher vertebrates. The term "mammal" includes, but is not limited to, a human. The dose of compound to be administered, in general, is from about 0.001 to about 5.0 mg/day; as usual, the daily dose may be administered in a single bolus, or in divided doses, depending on the judgment of the physician in charge of the case. A more preferred range of doses is from about 0.01 to about 2.0 mg/day; other dosage ranges which may be preferred in certain circumstances are from about 0.005 to about 2.0 mg/day; from about 0.1 to about 2.0 mg/day; from about 0.05 to about 0.8 mg/day; and a particularly preferred range is from about 0.05 to about 2.0 mg/day. It will be understood that the dose for a given patient is always to be set by the judgment of the attending physician, and that the dose is subject to modification based on the size of the patient, the lean or fat nature of the patient, the characteristics of the particular compound (freebase or salt) chosen, the severity of the patient's symptoms and psychological factors which may affect the patient's physiological responses.

Pharmaceuticals are substantially always formulated into pharmaceutical dosage forms, in order to provide an easily controllable dosage of the drug, and to give the patient an elegant and easily handled product.

While it is possible to administer 4-chloro-5-(imidazoline-2-ylamino)-6-methoxy-2-methylpyrimidine

directly, it is preferably employed in the form of a nonimmediate (sustained) release pharmaceutical formulation comprising one or more pharmaceutically acceptable carriers, diluents or excipients and the compound or a pharmaceutically acceptable salt thereof. Such formulations will contain, by weight, from about 0.01 percent to about 99 percent of the compound.

In making the formulations of the present invention, the active ingredient will usually be mixed with at least one carrier, or diluted by at least one carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container using conventional techniques and procedures for the preparing of pharmaceutical formulations. When the carrier serves as a diluent, it may be a solid, semi-solid or liquid material which acts as a vehicle, excipient or medium for the active ingredient. Thus, the formulations can be in the form of tablets, granules, pills, powders, lozenges, sachets, cachets, elixirs, emulsions, solutions, syrups, suspensions, aerosols (as a solid or in a liquid medium) and soft and hard gelatin capsules.

Examples of suitable carriers, diluents and excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, liquid paraffin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, tragcanth, gelatin, syrup, methylcellulose, methyl- and propyl-hydroxybenzoates, vegetable oils, such as olive oil, injectable organic esters such as ethyl oleate, talc, magnesium stearate, water and mineral oil. The formulations may also include wetting agents, lubricating, emulsifying and suspending agents, preserving agents, sweetening agents, perfuming agents, stabilizing agents or flavoring agents. The formulations of the invention are formulated so as to provide nonimmediate release of the active ingredient, by procedures well-known in the art. The formulations of the present invention are formulated to provide nonimmediate

release of the active ingredient for oral or implantable administration.

In nonimmediate release dosage forms, release of the drug from its dosage form is the rate limiting step in the release-absorption-elimination kinetic scheme. This is distinguished from the immediate release dosage forms where absorption of drug across a biological membrane is a rate limiting step. Nonimmediate release delivery systems have been divided into four categories: (1) delayed release; (2) sustained release; (3) site-specific release; and (4) receptor release.

Generally, delayed release systems are those that employ repetitive, intermediate dosing of a drug from one or more immediate release units incorporated into a single dosage form. Examples of delayed release systems include repeat action tablets and capsules and enteric-coated tablets where timed release is achieved by a barrier coating.

Sustained release delivery systems include both controlled release and prolonged release. Generally, sustained release systems include any drug delivery system that achieves slow release of drug over an extended period of time. When the system maintains relatively constant drug levels in the blood or target tissue it is considered a controlled release system. Where the system extends the duration of action over that afforded by a conventional delivery system, it is considered a prolonged release system.

Site-specific and receptor release systems refer to targeting of a drug directly to a desired biological location. In the case of site-specific release, a target is a particular organ or tissue. Analogously, in the case of receptor release, the target is the particular receptor for a drug within a particular organ or tissue.

Typical oral nonimmediate release forms include diffusional systems and dissolution systems. In diffusional systems, the release rate of drug is determined by its

diffusion through a water-insoluble polymer. There are generally two types of diffusional devices, reservoir devices in which a core of drug is surrounded by polymeric membrane; and matrix devices in which dissolved or dispersed drug is distributed substantially uniformly and throughout an inert polymeric matrix. In actual practice, many systems that utilize diffusion may also rely to some extent on dissolution to determine the release rate.

Common practices utilized in developing reservoir systems include microencapsulation of drug particles and press-coating of whole tablets or particles. Frequently, particles coated by microencapsulation form a system where the drug is contained in the coating film as well as in the core of the microcapsule. Drug release typically includes a combination of dissolution and diffusion with dissolution being the process that controls the release rate. Common material used as the membrane barrier coat, alone or in combination, are hardened gelatine, methyl and ethylcellulose, polyhydroxymethacrylate, hydroxypropylcellulose, polyvinylacetate, and various waxes.

In matrix systems, three major types of materials are frequently used in the preparation of the matrix systems which include insoluble plastics, hydrophilic polymers, and fatty compounds. Plastic matrices which have been employed include methyl acrylate-methyl methacrylate, polyvinyl chloride and polyethylene. Hydrophilic polymers include methyl cellulose, hydroxypropylcellulose and sodiumcarboxymethylcellulose. Fatty compounds include various waxes such as carnauba wax, and glyceryl tristearate. Preparation of these matrix systems are by methods well known to those skilled in the art. These methods of preparation generally comprise mixing the drug with the matrix material and compressing the mixture into tablets. With wax matrixes, the drug is generally dispersed in molten wax, which is then congealed, granulated and compressed into cores. As with other nonimmediate systems, it is common for a portion of the drug to be available

immediately as a priming dose and the remainder to be released in a sustained fashion. This is generally accomplished in the matrix system by placing a priming dose in a coat on the tablet. The coat can be applied by press coating or by conventional pan or air suspension coating.

Dissolution systems generally are products that have a decreased dissolution rate where the drug is highly soluble. Several approaches to achieving a slow dissolution rate include preparing an appropriate salt or derivative of the active agent, by coating the drug with a slowly dissolving material, or by incorporating the drug into a tablet with a slowly dissolving carrier. Encapsulated dissolution systems are prepared either by coating particles or granules of drug with varying thickness' of slowly soluble polymers or by microencapsulation. The most common method of microencapsulation is coacervation, which involves addition of a hydrophilic substance to a coloidal dispersion. The hydrophilic substance, which operates as the coating material, is selected from a wide variety of natural and synthetic polymers including shellacs, waxes, starches, cellulose acetate, phthalate or butyrate, polyvinylpyrrolidone, and polyvinyl chloride. After the coating material dissolves, the drug inside the microencapsule is immediately available for dissolution and absorption. Drug release, therefore, can be controlled by adjusting the thickness and dissolution rate of the coat. For example, the thickness can be varied from less than one μm to 200 μm by changing the amount of coating material from about 3 to about 30 percent by weight of the total weight. By employing different thickness', typically three of four, the active agent will be released at different, predetermined times to afford a delayed release affect. Coated particles can, of course, be directly compressed into tablets or placed into capsules.

Matrix dissolution systems are prepared by compressing the drug with a slowly dissolving polymer carrier into a tablet. Generally there are two methods for

preparing drug-polymer particles, congealing and aqueous dispersion methods. In the congealing method, the drug is mixed with a polymer or wax material and either cooled or cooled and screened or spray-congealed. In the aqueous dispersion method, the drug-polymer mixture is simply sprayed or placed in water and the resulting particles are collected.

Osmotic systems are also available where osmotic pressure is employed as the driving force to afford release of a drug. Such systems generally consist of a core of drug surrounded by a semipermeable membrane containing one or more orifices. The membrane allows diffusion of water into the core, but does not allow release of the drug except through the orifices. Examples of materials used as the semipermeable membrane include polyvinyl alcohol, polyurethane, cellulose acetate, ethylcellulose, and polyvinyl chloride.

A further system comprises ion-exchange resins. These resins are water-insoluble cross-linked polymers containing salt forming groups in repeating positions on the polymer chain. The active agent is bound to the resin by repeated exposure of the resin to the drug in a chromatographic column, or by prolonged contact of the resin with a solution of the drug. Drug release from the drug-resin complex depends on the ionic environment; that is pH and electrolyte concentration within the gastrointestinal tract, as well as the specific properties of the resin. Drug molecules attached to the resin are released by changing with appropriately charged ions in the gastrointestinal tract followed by infusion of the free drug molecule out of the resin. Generally, the rate of diffusion is controlled by the area of diffusion, diffusional path link, and extent of crosslinking in the resin. A further modification of the release rate can be afforded by coating the drug-resin complex.

The most common types of dosage forms used for parenteral nonimmediate release drug therapy are

intramuscular injections, implants for subcutaneous tissues and various body cavities, and transdermal devices. Generally, intramuscular injections involve a formation of a dissociable complex of a drug with another molecule. In this sense, the drug-molecule complex serves as a reservoir at the site of injection for drug release to the surrounding tissues. Examples of macromolecules include biological polymers such as antibodies and proteins or synthetic polymers such as polyvinylpyrrolidone, and polyethylene glycol.

Complexes can also be formed between drugs and small molecules. When the drug molecule is large relative to the complexing agent, the association constant will be greater and the complex more stable. Examples for smaller molecules include zinc, optionally suspended in a gelatin solution or an oil solution. An alternative dosage form for an intramuscular injection is an aqueous suspension. By varying viscosity and particle size a stable suspension of active ingredient can be afforded. Another common approach to decreased dissolution rate is to decease the saturation solubility of the drug. This is accomplished through the formation of less soluble salts and prodrug derivatives and by employing polymorphic crystal forms of the active ingredient.

Another approach is a use of oil solutions and oil suspensions. As will be appreciated by those skilled in the art, those drugs having appreciable oil solubility and the desired partition characteristics are most suitable for this approach. Examples of oils which may be used for intramuscular injection include sesame, olive, arachnis, maize, almond, cotton seed and caster oil. With oil suspensions, drug particles must first dissolve in the oil phase and then partition into the aqueous medium.

Emulsions comprising oil-in-water emulsions or water-in-oil emulsions may also be used.

Implants comprise a drug-barring polymeric device which is inserted subcutaneously or in various body

cavities. The polymer material which is used must, of course, be biocompatible and nontoxic and are typically chosen from among hydrogels, silicones, polyethylenes, ethylene-vinyl acetate copolymers, and biodegradable polymers. Hydrogels generally are a polymeric material that exhibit the ability to swell in water and retain greater than 20 percent of that water within its structure, but which will not dissolve in water. Small molecular weight substances are capable of diffusing through hydrogels. Specific example of hydrogels include polyhydroxyalkyl methacrylates, polyacrylamide and polymethacrylamide, polyvinylpyrrolidone, polyvinyl alcohol, and various polyelectrolyte complexes.

Additional implantable systems include subcutaneous devices, and intravaginal devices.

Percutaneous drug absorption, more commonly referred to as transdermal systems, generally includes the use of microporous membranes as the rate controlling barrier. Microporous membranes are films varying in thickness with pore sizes ranging from several micrometers to a few angstroms. Examples of material from which such membranes are made include regenerated cellulose, cellulose nitrates/acetate, cellulose triacetate, polypropylene, polycarbonate and polytetrafluoroethylene. The barrier properties of these various films depend upon the method of preparation, the medium with which the pores are filled, pore diameter, percent porosity, and tortuosity.

An example of a transdermal system is disclosed in U.S. Patent 4,201,211.

Targeted delivery systems include nanoparticles and liposomes. Nanoparticles are examples of systems known collectively as colloidal drug delivery systems. Other members in this group include microcapsules, nanocapsules, macromolecular complexes, polymeric beads, microspheres and liposomes. Generally, a nanoparticle is a particle containing dispersed drug with a diameter of 200-500 nm. Materials used in the preparation of nanoparticles are

sterilisable, nontoxic and biodegradable. Examples include albumen, ethylcellulose, casein and gelatin. Typically, they are prepared by procedures similar to the coacervation method of microencapsulation.

Liposomes, generally, are phospholipids that when dispersed with aqueous media swell, hydrate and form multilamellar concentric bilayer vesicles with layers of aqueous media separating the lipid bilayers. Phospholipids can also form a variety of structures other than liposomes when dispersed in water depending on the molar ration of lipid to water. At low ratios, the liposome is the preferred structure. The actual physical characteristics of the liposomes depend on pH, ionic strength and the presence of divalent cations. They show low permeability to ionic and polar substances but at elevated temperatures undergo a phase transition which alters their permeability. Polar drugs are trapped in the aqueous spaces and nonpolar drugs bind to the lipid bilayer of vesicle. Polar drugs are released when the bilayer is broken or by permeation, but nonpolar drugs remain affiliated with the bilayer until it is disrupted by temperature or exposure to lipoproteins. The liposome, of course, acts as the carrier or the active agent.

Depending on the method of administration, the formulations of the present invention may be formulated as nonimmediate (i.e. sustained) release tablets, capsules, injection solutions for parenteral use, gel, suspensions or elixirs for oral use or suppositories. Preferably the compositions are formulated in a unit dosage form, each dosage containing an amount of active ingredient suitable to afford a subject from 0.01 to 3.0 mg, more usually 0.05 to 2.0 mg, of the active ingredient. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic or prophylatic effect, related to the desired daily or divided dose, in

association with one or more suitable pharmaceutical carriers, diluents or excipients therefore to afford sustained release of active agent. With the sustained release formulation, the unit dosage form may contain from 0.01 to 5.0 mg of the active ingredient. A preferred formulation of the invention is an oral or implantable nonimmediate release formulation comprising 0.01 to 3.0 mg or 0.05 to 2.0 mg of active ingredient together with a pharmaceutically acceptable carrier therefor in a unit dosage form. Most preferred is an oral nonimmediate release formulation.

The nonimmediate release formulations of the present invention should provide a prophylatic or therapeutic amount of moxonidine to a patient to achieve, and then maintain, an effective dose of active agent with diminished undesirable effects. These formulations should achieve a more idealized spatial placement and temporal delivery of moxonidine, particularly temporal delivery. Spatial placement, of cource, relates to targeting a pharmaceutical agent to a specific organ or tissue while temporal delivery refers to controlling the rate of drug delivery.

Nonimmediate release formulations of the present invention should afford one or more of the following advantages over the known immediate release formulations: 1) minimize or eliminate patient compliance problems; 2) employ less total active agent; 3) minimize or eliminate local side effects; 4) minimize or eliminate systemic side effects; 5) afford less potentiation or reduction in active agent activity with chronic use; 6) minimize active agent accumulation with chronic use; 7) improve efficiency in treatment; 8) control the condition more promptly; 9) reduce fluctuation in drug level affording improved control of the condition; and 10) economy.

Patent compliance, of course, is a necessary and important component in the success of all self-administered drug therapy.

It is anticipated the nonimmediate release formulations of the present invention will afford more constant drug levels. In healthy humans, a geometric mean for time to maximum plasma concentration (t_{max}) should be from about 2.5 hours to about 5.0 hours, preferably 2.5 - 4.0 hours, with a geometric mean plasma elimination half-life of from about 6.0 hours to about 16.0 hours, preferably 7.0 - 15.0 hours. Thus, be employing the nonimmediate release unit dosage forms described herein, once-a-day or twice-a-day administration is contemplated.

Moxonidine is currently commercially available in at least Germany and Austria as 0.2, 0.3 and 0.4 mg dosage immediate release formulation tablets as an antihypertensive agent. Set forth below is the complete formulation of the currently marketed 0.3 mg tablet. For the 0.2 mg and 0.4 mg tablet, the amount of lactose is adjusted to accommodate the higher or lower active ingredient content.

FORMULATION - PRODUCT DESCRIPTION

Pale red film-coated tablet 105 mg containing 0.3 mg of moxonidine as active ingredient.

Active Ingredients	[mg]
Moxonidine	0.30
Other Ingredients	
Lactose	95.700
Povidone	0.700
Crospovidone	3.000
Magnesium Stearate	0.300
Hydroxypropyl Methylcellulose 2910	1.300
Ethylcellulose Agueous	1.200
Polyethylene Glycol 6000	0.250
Talc	0.975
Red Ferric Oxide	0.025
Titanium Dioxide	1.250

The current commercial formulations of moxonodine afford quick, immediate, release of active agent having a geometric mean t_{max} of 0.5 - 3.0 hours with a geometric mean plasma elimination half-life of 2.0 - 3.5 hours.

In order to more fully illustrate this invention, examples of formulations believed to be useful with moxonidine are provided below. The examples are illustrative only and are not intended to limit the scope of the invention. Sustained release formulations believed to be useful for the present invention are disclosed in U.S. Patent Nos. 4,140,755; 4,218,433; 4,389,393; 4,839,177; 4,865,849; 4,892,742; 4,933,186 and 5,422,123. The most preferred formulations are those disclosed in U.S. Patent No. 5,422,123.

Clinical Protocol and Results

Data on the pharmacokinetics and pharmacodynamics of moxonidine vs. placebo has been obtained in patients with congestive heart failure. Changes in standing systolic blood pressure (SSBP) and changes in plasma norepinephrine concentration (PNE) in the moxonidine and placebo groups were used to evaluate the effects of moxonidine and to predict appropriate dosing strategies. Previous reports have suggested that administration of up to 0.6 mg moxonidine to patients with essential hypertension (HTN) can produce significant reductions in blood pressure 24 hours after dosing, without an excessive incidence of symptomatic hypotension. The pharmacokinetics and pharmacodynamics in CHF patients are compared to a previous report in patients with essential hypertension following a single 0.25 mg dose (Kirch et al., J. Clin. Pharmacol, 30, 1088-1095 (1990)).

Protocol

Summary of Study Design

Moxonidine was administered in a randomized, double-blind, placebo-controlled Phase 2 clinical trail in patients with functional New York Heart Association (NYHA) Class II-III CHF. Only patients receiving a stable dose of an angiotensin converting enzyme ACE inhibitor or who failed previous ACE therapy were eligible. Patients could also be receiving digitalis, diuretics and other drugs used as CHF therapy, provided the dose was stable prior to start of the study. The study consisted of a 2-week single-blind screening period, a 4-week double-blind dose progression period, and an 8-week, double-blind maintenance period.

Patients were included in the study only if they meet all of the following criteria:

[1] Patients with clinically stable, chronic, moderately severe NYHA Class II-III CHF.

[2] Men or women between the ages of 21 and 79 years.

[3] Patients with left ventricular ejection fraction of ^{2}40%, evaluated by radionuclide angiocardiography, quantitative echocardiography, or angiocardiogaphy within 1 month prior to study entry.

[4] Patients would be receiving or have previously failed ACE inhibitor therapy for CHF. Patients may be taking digitalis or diuretics or both. Doses of digitalis, diuretics, and other drugs used as CHF therapy will have been stable for at least 2 weeks.

Patients were excluded from the study for any of the following reasons:

[1] Myocardial infarction in the last 90 days.

[2] Hemodynamically significant primary valvular or outflow tracto obstruction (for example, mitral valvular stenosis, aortic valvular stenosis, asymmetrical septal hypertrophy, or malfunctioning prosthetic valve), severely reduced diastolic function, or complex congenital heart disease.

[3] Active myocarditis.

[4] Syncopal episodes presumed to be life-threatening arrhythamias (asymptomatic cardiac arrhythmia's, including nonsustained ventricular tachycardia, are not an exclusion criterion).

[5] Likelihood of cardiac surgery, including transplantation, in the near future.

[6] Unstable angina pectoris (defined as angina at rest) or severe stable angina (more than two attacks per day on average) despite treatment.

[7] Systolic blood pressure ^{2} 90 mm Hg (measured

after 10 minutes of recumbency) or symptomatic hypotension.

[8] Uncontrolled hypertension (systolic blood pressure ³ 180 mm Hg and diastolic blood pressure ³ 105 mm Hg) at entry, measured after 10 minutes of recumbency.

[9] Advanced pulmonary disease (FEV_1/FVC ²50 peak, expectory flow rate <200 mL/sec, or FVC <60% of predicted) or cor pulmonale.

[10] Cerebrovascular disease (for example, significant cartotid artery stenosis) that could potentially be complicated or rendered unstable by a reduction in blood pressure.

[11] Collagen vascular disease other than rheumatoid arthritis (for example, systemic lupus erythematosus, polyarteritis nodosa, scleroderma).

[12] Suspected significant renal artery stenosis, or severely reduced renal function (that is, creatinine >160μM/L).

[13] Malignancies, except for surgically cured skin cancer, carcinoma-in-situ, or 5 years' freedom of disease after the diagnosis of solid tumors.

[14] Requirement for immunisuppressive therapy (the use of steroids for non-life-threatening diseases such as arthritis is not an exclusion).

[15] Likelihood of a prospective participant being nonadherent for reasons such as chronic alcoholism, lack of a fixed address, or drug addiction.

[16] Significant primary liver disease.

[17] Other life-threatening disease or condition such that prospective participant is not realistically expected to complete the trial.

[18] Pregnant woman or woman of childbearing

potential who is not protected from pregnancy by an acceptable method.

[19] Use of beta-blockers within the last 3 months.

[20] Previous exposure to moxonidine within one month.

[21] Concomitant use of other investigational drugs.

[22] Previous participation in this trial.

Exclusion criteria must be satisfied at entry into the study and at Visit 3 (randomization). In addition, patients were excluded from the study if the following criterion is met at Visit 3 (randomization):

[23] Unjustified lack of compliance with placebo medication between Visits 1 and 3 (<90% of prescribed medication).

Dosage groups for the trial were studied sequentially. Six moxonidine dosage groups were evaluated. Dosage groups were defined by a starting level of moxonidine and up to two dosage increases at 1-week intervals. The study drug was given initially on a once-a-day regimen.

) The sequential study periods are defined as follows:

- <u>Screening (single-blind, 2 weeks)</u>: Eligibility assessment and compliance with placebo medication.
- <u>Dose Progression (double-blind, 4 weeks)</u>: Administration of the first does of the study drug followed by up to two dosage increases at 1-week intervals.
- <u>Maintenance (double-blind, 8 weeks)</u>: Two visits at 4-week intervals during which the dose of moxonidine was constant at the highest dose.

A week is defined as 5 to 9 days.

For each individual patient, the progression of the study periods is illustrated in Table 1.

Table 1

Study Period Progression per Patient

Variable	Screening	Dose Progression	Maintenance
	Study Period		
Study Drug	Placebo	Placebo Moxonidine	Placebo Moxonidine
Dose Step		1,2,3	3
Duration	2 Weeks	4 Weeks	8 Weeks
Visit Number	1,2	3[a],4[b],5[b],6[a]	7[c],8[a,c]

[a]8-hour evaluation day (Study Day).
[b]4-hour evaluation day (Stage I only).
[c]Visits 7 and 8 may be deleted during Stage I.

Visits 3, 6, and 8 are 8-hour evaluation days (referred to as Study Days 1, 2, and 3), on which the daily dose of study medication was withheld until administration at the medical clinic, after which the patients were followed up for 8 hours. During that time, physiologic observations were made, adverse events elicited, and blood samples drawn for clinical laboratory measurements and neuroendocrine mediator and study drug concentration assays. At Visits 4 and 5, the patients received their medication dose in the medical clinic and remained for observation in the clinic for 4 hours following dosage administration.

During the study, the six Moxonidine dosage groups were studied sequentially, beginning with Dosage Group 1. For each dosage group, 2 patients were randomly assigned to active study medication and one to placebo. It is assumed that three patients entered the study each week. The study ended when patients randomly assigned to moxonidine Dosage Group 6 or

placebo completed Visit 8 (the end of the dose maintainance period), after which patients were discontinued.

The dosage size was progressively larger from the first to the sixth group. For each group the starting dose was smallest, with a maximum of two subsequent dose progression steps at 1-week intervals.

Table 2

Moxonidine Dose Steps in mg/day by Dosage Group

Dose Step		Moxonodine Dosage Group 1	2	3	4	5	6
Start	1	0.1	0.1	0.1	0.1	0.2	0.2
Middle	2	0.1	0.2	0.2	0.3	0.3	0.4
Final	3	0.1	0.2	0.3	0.4	0.6	0.6

The dosing sequence is presented in Table 3.

Table 3

Moxonidine Dosing Sequence

Dosage Group[a]	Week Number 0	1	2	3	4	5	6	7	8	9
1	0.1mg	0.1mg	0.1mg[b]		*0.1mg[c]*					
2		0.1mg	0.2mg	0.2mg[b]		*0.2mg[c]*				
3			0.1mg	0.2mg	0.3mgb		*0.3mg[c]*			
4				0.1mg	0.3mg	0.4mg[b]		*0.4mg[c]*		
5					0.2mg	0.3mg	0.6mg[b]		*0.6mg[c]*	
6						0.2mg	0.4mg	0.6mg[b]		*0.6mg[c]*

[a] Two patients were randomly assigned to active study medication and one to placebo per group.
[b] Patients took the highest dose for 2 weeks.
[c] Patients were maintained for an additional 8 weeks on the highest dose of moxonidine for the dosage group.

Dosage and Administration

Materials and Supplies

Moxonidine and placebo tablets were provided to the hospital pharmacy and dispensed to patients in a number sufficient for each visit interval. Tablets of 0.1 mg of moxonidine and tablets of placebo were identical in appearance and combined in the proper proportions to assure desired dosages (including twice daily dosing if required), ease of compliance, and maintenance of the blind. The term "dose" in this protocol refers to the combination of study drug tablets taken on a single day. The current commercial formulations were used with lactose content adjusted to accommodate the presence or absence of active ingredient as described above.

Screening

Patients were administered the first dose of placebo at the medical clinic, and at Visits 1 and 2 were given a sufficient supply of placebo medication for once-daily dosing. Study drug was be taken once a day early in the morning as a single dose (6 tablets).

Dosing Progression and Maintenance

After randomization at Visit 3, each patient was administered one dose of moxonidine (0.1 or 0.2 mg) or placebo during Visit 3. Visit 3 (Study Day 1) is one of the three 8-hour evaluation days during this protocol on which study medication was taken at the medical clinic and the patient was followed up for 8 hours for safety assessments and laboratory measurements. In addition, at Visits 4 and 5, the medication dose was administered at the medical clinic and patients were observed for four hours following administration of the medicine dose. Visits 6 and 8 (Study Days 2 and 3) were also 8-hour evaluation days at which the daily dose was withheld for administration at the medical clinic, after which the patient was followed for up to 8 hours. On each of the 4-hour and 8-hour evaluation days, patients did not take their daily

medication until administered at the medical clinic. At each Visits 3 through 7, patients were provided sufficient moxonidine or placebo medication for one-daily administration until the next visit.

Study drug or placebo was taken once a day early in the morning as a single dose (6 tablets), unless evidence of symptomatic hypotension justified dividing the dose, with the result that the regimen was twice daily.

Efficacy measures included the following:

- Plasma concentrations of neuroendocrine mediators (norepinephrine, N-terminal atrial natriuretic peptide).
- Vital signs (recumbent systolic and diastolic blood pressure and heart rate).
- Reduction in prescribed diuretic dosage.

Blood was drawn for the study drug plasma concentration analysis at approximately 0, 0.5, 1, 1.5, 2, 4, 6, and 8 hours after study drug administration on the three Study Days (Visits 3, 6, and 8). Plasma concentrations were determined using a gas chromatography/mass spectrometry analytical method. Generally, aliquots of human plasma (1.0 ml) are fortified with 25.0 µl (10 pg/µl working internal solution) of internal standard (Clonidine.HCl). Each sample is extracted into ethyl acetate under basic conditions, the organic layer is removed, and the plasma discarded. Samples are back extracted with 0.5 M HCl and the organic layer is discarded. Samples are then extracted into methylene chloride under basic conditions, the aqueous layer is discarded and the organic layer is taken to dryness under a stream of nitrogen. The dried sample residues are derivatized with 3,5 bis(trifluoromethyl) benzoyl chloride and again evaporated to dryness under nitrogen. Samples are reconstituted in 50 µl of acetonitrile, transferred to plastic gas chromatography autosampler vials and injected (1 µl) onto the GC/MS system.

Pharmacokinetics

Unless otherwise stated, "mean" indicates geometric mean. Plasma concentration-time profiles of the first dose (Visit 3) of 0.1 mg moxonidine in eight patients with CHF were prepared and evaluated. Absorption was rapid (mean t_{max}: 0.75 hours), and decline in plasma concentration was mildly biphasic. Mean oral clearance was 28.03 L/hr, and the mean elimination half-life was 3.28 hours.

Absorption of moxonidine was more rapid than previously reported for patients with hypertension (mean tmax: 1.07 hours). Oral clearance in CHF patients was lower and half-life was longer than in patients with hypertension (CL: 43.58 L/hr; t1/2: 2.01 hours). Differences in clearance and half-life between the populations may have been due to differences in age and renal function (mean age CHF: 69 yr; mean age HTN: 49 yr). More rapid absorption and increased half-life of moxonidine may produce an elevation in Cmax in the CHF population relative to HTN patients at comparable doses. Nevertheless, extrapolations based on Visit 3 concentrations of moxonidine in plasma predict negligible accumulation of moxonidine following repeated administration to CHF patients, even with a BID regimen. Predicted peak to trough rations for BID dosing is 20:1.

Previous data demonstrated a temporal displacement between peak concentration of drug in plasma (1 hr) and maximum effect (4-6 hr) in HTN patients. Also, duration of effect is much longer than predicted from half-life in plasma. Both observations suggest that drug in plasma equilibrates slowly with the effect site in the CNS.

Pharmacodynamics

Change in Standing Systolic Blood Pressure (SSBP) from Baseline (T=0) to 2 hr on Visit 3, Stage I

Table 4

	Standing Systolic Blood Pressure	
Patient Number	Absolute Change	Percent Change
Placebo		
101	-10	-8.3
107	-10	-10
201	25	21.7
205	10	7.7
301	20	15.4
303	5	5.0
Mean	6.7	5.2
Moxonidine 0.1mg		
102	10	7.7
103	-60	-42.8
104	10	7.7
105	-10	-10
202	0	0
203	0	0
206	-10	-6.9
302	-15	-12
307	-5	-4.3
Mean	-8.9	-6.7

Table 4 shows the absolute and percentage changes from predose baseline in standing systolic blood pressure at Study Day 1 (visit 6). There were 6 patients who received placebo, and 9 who received moxonidine, 0.1 mg. The peak effect was at 2 hours after drug administration. A trend of increasing SSBP was observed in the placebo group (avg. 6.7 mm Hg). The

change may have been due to the decay of effect of the morning dose of ACE inhibitor taken prior to coming to the clinic. Compared to placebo, moxonidine produced a reduction in SSBP, the average difference being -15.6 mm Hg. (-11.9%).

Consistent with previous data in hypertensive (HTN) patients, a temporal displacement was observed between peak reduction in blood pressure and peak plasma concentration of moxonidine. However, time to peak effect (3 hours) in CHF patients was shorter than in patients with HTN (5 hours). Also, duration of blood pressure reduction in CHF patients was short, with a return of pre-dose SSBP eight hours after dosing. The short duration of action predicts negligible cumulation of effect following repeated QD or BID dosing.

Changes in Plasma Norepinephrine (PNE)

Table 5 shows the absolute and percentage changes in norepinephrine plasma concentration from predose baseline to 2 hours after dosing (0.1 mg) in the groups of patients. These values are obtained using standard clinical laboratory procedures.

Table 5

Change in Norepinephrine from Baseline (t=0) to 2 hr on Visit 3, Stage I

Patient Number	Norepinephrine Absolute Change	Percent Change
Placebo		
101	40	6.7
107	144	40.9
201	48	23.5
205	104	15.1
301	40	10.6
303	-124	-16.8
Mean	42.0	13.3

Moxonidine 0.1mg		
102	-62	-27.7
103	-168	-30.1
104	-142	-37.2
105	-360	-42.1
202	-92	-17.1
203	-6	-1.8
206	-50	-15.2
302	24	6.9
307	22	9.6
Mean	-92.7	-17.2

Moxonidine at 0.1 mg, produced a maximum reduction in mean PNE 2 hours after dosing at Visit 3. Two hours after dosing, PNE was reduced by over 30% relative to placebo. Duration of effect was short. PNE in the moxonodine group returned to baseline 4 hours after dosing. Effect of moxonidine on PNE on Visits 3 and 6 in a representative subject demonstrated the patient did not respond to a 0.1 mg dose on Visit 3, but responded intensely to a 0.3 mg dose in Visit 6. However, pre-dose PNE on Visit 6 was elevated relative to baseline. Similarly, Visit 6 baseline PNE was elevated relative to Visit 3 baseline PNE in 5 of 8 patents receiving moxonidine, but only 1 of 5 subjects receiving placebo.

Time to maximum PNE reduction in CHF patients (2 hours) was shorter than reported for HTN patients (6 hours). The short duration of effect in CHF patients suggests that QD dosing and BID dosing of moxonidine will not sustain suppression of PNE over a 24-hour interval. The PNE time course in a representative subject following 0.1 mg moxonidine BID was nearly superimposable with the time course following the administration of the first 0.1 mg dose (Visit 3).

Administration of immediate-release moxonidine 0.1-0.6 mg QD or 0.1-0.2 mg BID to CHF patients failed to produce a sustained reduction in sympathetic activity over the dosing interval, although a large transient reduction was observed 1

- 3 hours after dosing in many subjects. Ideally, the dosing regimen should produce a significant suppression of PNE at trough following chronic dosing, without excessive reductions in blood pressure at time of peak effect. These objectives would possibly be accomplished with the current commercial immediate release formulation by increasing the daily dose (beyond 0.6 mg/day) and reducing the dosing interval. However, a 4-8 hour duration of effect following a 0.1-0.6 mg dose suggests that the optimum dosing interval would be at least QID. However, QID dosing may be impractical as patient compliance is a problem, and may still be associated with high peak to trough effect ratios. For example, patient noncompliance with a multiple dosing regimen can result in a failure to obtain the benefits of the active agent and may exacerbate the high peak to trough effect ratios.

Based on the above, and additional data not set forth herein, administration of moxonidine via a nonimmediate release formulation is required to provide a practical method of sustaining sympathetic suppression while lowering peak to trough ratios. Since symptomatic hypotension may be precipitated by the sharp and transient reduction in sympathetic activity that is observed 1-3 hours after moxonidine administration, the side-effect profile of moxonidine should also be improved by a nonimmediate release formulation.

The following examples will further illustrate the present invention.

Composition of the Formulas

Example 1

		mg/Tbl
Inside Powder	Moxonidine	0.535
	HPMC 2910, 3mPas	0.565
	Calcium phosphate	27.80
	Lactose	27.80
Outside Powder	HPMC 2208	42.90
	Magnesium stearate	0.40
Coating	None	
Total Mass		100.00

The sustained release of the active compound is based on the principle of a hydrocolloid matrix. The matrix is formed by hydroxypropylmethylcellulose, HPMC 2208 (15000 mPas, at 2%, 20°C). A mixture of Lactose and Calcium phosphate was used as carrier.

The liberation of the active compound was controlled by varying the ratios between these three components.

The batch analysis tests showed a high sensitivity of the formula to variations of the mixing time. Increased mixing times tend to lead to an uneven lubricant distribution which caused insufficient tablet hardness.

Example 1

<u>The Manufacturing Steps</u>

mixing of the inside powder in a planetary mixer;

granulation;

tray drying at 50°C overnight;

dry milling by using an oscillating granulator, sieve-1 mm;

addition of the outside powder and 30 min tumble mixing; and

compression.

Example 1

Batch Analysis

Parameter	
Batch size	1000 g
Mass uniformity (min. - max.; average)	97.0 - 103.0 mg; average = 100.0 mg
Assay average	average = 0.5173 mg
Hardness	67 - 76 N
Dissolution: (In-vitro) (Ph. Eur. 2nd Ed. V.5.4, paddle apparatus, Figure 1, 900mL water at 37deg C, 100 rpm)	2 h: 36.2% 4 h: 62.9% 8 h: 96.9%

Example 2

	Eyetablet	mg/Tbl
Inside Powder	Moxonidine	0.535
	HPMC 2910, 3 mPas	0.550
	Calcium phosphate	27.800
	Lactose	27.615
	HPMC 2208	4.900
	Ethanol	15.000
	Water	3.000
	Methylene dichloride	15.000
Outside Powder	HPMC 2208	38.000
	Magnesium stearate	0.600
Coating	Polyethylene Glycol 20000	0.454
	HPMC 2910, 3 mPas	0.906
	Talc	0.280
	Titanium dioxide	0.120
	Azorubine E 122	0.240
Inside Powder of the Coat	Moxonidine	0.100
	Lactose	177.900

	Povidone	1.400
	Ethanol	16.000
	Water	3.200
	Methylene dichloride	16.000
Outside Powder of the Coat	Corn starch	10.000
	Crospovidone	10.000
	Magnesium stearate	0.600
External Coating	Polyethylene Glycol 20000	1.34
	HPMC 2910, 3 mPas	3.14
Total Mass		304.00

Eyetablet (0.635 mg)

Because of the delayed therapeutic effect with Example 1 (data not included), it was decided to combine a sustained release formulation with an initial dose. As data demonstrated (not included here), compared to the moxonidine standard immediate release tablet, a significant blood pressure decrease was noted one hour after dosing.

The "Eyetablet" is a special kind of presscoated tablet: A circular biconvex kernel (6 mm in diameter) is pressed into a circular coat "U" shaped in cross-section and 9 mm in diameter, without the kernel being completely covered.

The coat contains the initial dose (0.1 mg) in an immediate release form. It disintegrates within 30-95 seconds because of a high content of disintegration enhancers (Crospovidone 5%, Corn starch 5%).

The kernel carries the sustained form (0.535 mg). A small quantity of the HPMC 2208 (max. 5%), which is required for the sustained release, was incorporated as carrier into the inside powder, facilitating uptake of sufficient amount of liquid for granulation.

The tablets were coated for humidity protection.

Example 2

The Manufacturing Steps

Moxonidine-Eyetablet

mixing of the inside powder in a planetary mixer;

granulation;

tray drying at 50°C overnight;

dry milling using an oscillating granulator, sieve-0.75 mm;

addition of the outside powder and 30 min tumble mixing (HPMC 20 min + Magnesium stearate 10 min);

compression;

coating of the kernels with a 15% suspension by means of a spray gun (0.8 mm nozzle);

mixing of the inside powder in a planetary mixer;

granulation;

tray drying at 50°C overnight;

dry milling by using an oscillating granulator, sieve-0.75 mm;

addition of the outside powder and 30 min tumble mixing;

compression; and

coating of the kernels with a 10% suspension by means of a spray gun (0.8 mm nozzle).

Example 2

Batch Analysis

Parameter	Moxonidine-Eyetablet
Batch size	5000 g
Mass uniformity (min. - max.; average)	293.2 - 309.2 mg; average = 303.8 mg
Assay average	average = 0.6236 mg
Hardness	36 - 48 N
Disintegration time	30 - 95 s (coat)
Dissolution: (in vitro) (Ph. Eur. 2nd Ed. V.5.4, paddle apparatus, Figure 1, 900mL water at 37deg C, 100 rpm)	2 h: 52.6% 4 h: 73.0% 8 h: 96.4%

Using procedures substantially similar to those described below for Example 3-6, the formulations of Examples 3-1 through 3-5 were prepared and coated as described in 3-6.

Example 3-1

Moxonidine	0.5%
Povidone	-
Calcium phosphate	37.7%
Lactose	37.7%
HPMC 2208	23.5%
Mg-stearate	0.6%

Example 3-2

Moxonidine	0.5%
Povidone	0.5%
Calcium phosphate	37.7%
Lactose	37.7%
HPMC 2208	18%
Mg-stearate	0.6%

Example 3-3

Moxonidine	0.5%
Povidone	0.5%
Calcium phosphate	86.4%
Lactose	-
HPMC 2208	12%
Mg-stearate	0.6%

Example 3-4

Moxonidine	0.5%
Povidone	0.5%
Calcium phosphate	91.4%
Lactose	-
HPMC 2208	7.0%
Mg-stearate	0.6%

Example 3-5

Moxonidine	0.5%
Povidone	0.5%
Calcium phosphate	88.4%
Lactose	-
HPMC 2208	10.0%
Mg-stearate	0.6%

Example 3-6

		mg/Tbl
Inside Powder	Moxonidine	0.5
	Povidone	0.625
	Calcium phosphate	110.625
Outside Powder	HPMC 2208	12.500
	Magnesium stearate	0.750

Coating	Polyethylene Glycol 6000	0.25
	HPMC 2910, 6 mPas	1.30
	Talc	1.00
	Titanium dioxide	1.225
	Ferric oxide, yellow	0.025
	Aqueous Ethylcellulose dispersion 30%	1.200
Total Mass		130.00

Example 3

The Manufacturing Steps

mixing of the inside powder in a planetary mixer;

granulation;

tray drying at 50°C overnight;

dry milling by using an oscillating granulator, sieve-1mm;

addition of the outside powder and 30 min tumble mixing;

compression; and

aqueos coating of the kernels with a 12.5% suspension by means of a spray gun (0.8 mm nozzle).

Examples 3-6

Batch Analysis

Parameter	
Batch size	2000 g
Mass uniformity (min. - max.; average	128.9 - 132.3 mg; average - 130.2 mg

Assay range; average	0,492-0,539 mg (min. - max.) average = 0.513 mg
Hardness	77 - 80 N
Dissolution: (in vitro) (Ph. Eur. 2nd Ed. V.5.4., paddle apparatus, Figure 1, 900mL water at 37deg C, 100 rpm)	2 h: 66.0% 4 h: 85.7% 8 h: 108.9%

The formulations of Examples 1, 2 and 3-6 were evaluated in limited clinical studies in patients with hypertension (data not included).

	Comparative Example A; 0.25 mg moxondine immediate release	mg/Tbl
Inside Powder	trituration of 1% Moxonidine in Lactose (special grade) Povidone Lactose	20.0 0.7 96.0
Outside Powder	Crospovidone Magnesium stearate	3.0 0.3
Coating	Polyethylen Glycol 6000 HPMC 2910, 3 mPas Talc Titanium dioxide Ferric oxide, red Aqueous Ethylcellulose dispersion 30%	0.25 1.30 0.9975 1.25 0.0025 1.20
Total Mass		125.00

The formulation of Example 1 was compared to a 0.25 mg immediate release tablet (Comparative Example A) in a study with eight hypertensive patients. Plasma concentrations were determined using known GC/MS methodology.

With the formulation of Example 1, the maximum plasma concentration was reached 2-3 hours after administration. The

higher dose, compared to Example A, caused a 60% increase of the plasma concentration maxima (2.25 $\pm$ 1 ng). These kinetic data correspond to the blood pressure decrease. Example 1 led to a 50% higher maximum decrease of the systolic and the diastolic blood pressure compared to Example A, that occurred 5-6 hours after administration. The action period, defined as the period of time for which a diastolic blood pressure decrease greater than or equal to 10 mm Hg was not significantly different for both Moxonidine formulations. Also the degree of mouth dryness and tiredness were the same. Both formulations were well tolerated.

In a clinical study with four healthy volunteers the "Eyetablet" of Example 2 was compared to a 0.25 mg immediate release tablet (Comparative Example A) with regard to the kinetic behaviour. Plasma concentrations were determined using known GC/MS methodology. See for Example Kirch, et al., J.Clin. Pharmacol., 30, 1088-1095 (1990); Trenk, et al., J. Clin. Pharmacol., 27, 988-993 (1987); and Kirch, et al., Clinical Pharmacokinetics, 15, 245-253 (1988).

The "Eyetablet" provoked a 2.5 fold time period of a blood level above 1 ng/ml compared to Example A, while the maximum plasma concentration remained nearly constant. The onset of the effect was not substantially affected by the initial dose.

Because of the small number of patients and variability of the data, an evaluation of the parameter period of blood pressure decrease was not believed appropriate.

A study with two volunteers was carried out concerning only kinetic data of the Example 3-6 formulation which is reported below along with the limited clinical kinetic data obtained as described above.

Moxonidine-Formulations	t-max [hours]	c-max [ng/ml]	AUC [h * ng/ml]	Relative bioavailability*
Example A (0.25 mg)	1	1.35	7.42	not available
Example 1	4	2.25	18.49	109%
Example 2	1	1.48	10.30	72%
Example 3-6	1	1.22	7.41	not available

*The relative bioavailability was determined by calculating the theoretical AUC-value of the same dose in a standard form. AUC-value of the immediate release formulation = 100%

By substantially following the procedures described in U.S. Patent 5,422,123, which is incorporated by reference herein, in its entirety, Examples 4 (4-1 and 4-2), 5 and 6 were prepared as three-layer tablets.

Example 4-1

Global Compositions

Substance	mg/tablet
Moxonidine 1% in lactose	30.0
Glycerylbehenate (Compritol 888 ATO)	31.9
Lactose pulvis H_2O	78.13
Mg-stearate	3.0
Hydroxypropylmethylcellulose (Methocel E50)	38.25
Hydroxypropylmethylcellulose (Methocel K4M)	39.88
Hydroxypropylmethylcellulose (Methocel K100M)	60.0
Polyvinylpyrrolidone (Plasdone K29-32)	13.5
Colloidal Silicondioxide (Syloid 244)	2.0
Yellow ferric oxide	0.35

Total tablet weight: 297.01
Diameter (mm): 8
Thickness (mm): 6.2

Example 4-2

Global Compositions

Substance	mg/tablet
Moxonidine 1% in lactose	30.0
Glycerylbehenate (Compritol 888 ATO)	20.0
Lactose pulvis H_2O	56.5
Mg-stearate	3.0
Hydroxypropylmethylcellulose (Methocel E50)	-
Hydroxypropylmethylcellulose (Methocel K4M)	-
Hydroxypropylmethylcellulose (Methocel K100M)	170.0
Polyvinylpyrrolidone (Plasdone K29-32)	15.0
Colloidal Silicon Dioxide (Syloid 244)	2.0
Yellow ferric oxide	0.5

Total tablet weight: 297.0
Diameter (mm): 8
Thickness (mm): 6.2

Example 5

Global Composition

Substance	mg/tablet
	0.1 mg
Moxonidine 1% in lactose	10.0
Glycerylbehenate (Compritol 888 ATO)	27.0
Lactose pulvis H_2O	99.76
Mg-stearate	3.0
Hydroxypropylmethylcellulose (Methocel E50)	-
Hydroxypropylmethylcellulose (Methocel K4M)	79.76
Hydroxypropylmethylcellulose (Methocel K100M)	60.0
Polyvinylpyrrolidone (Plasdore K29-32)	15.0
Colliodal Silicon Dioxide (Syloid 244)	2.0
Yellow ferric oxide	0.5

Total tablet weight: 297.02
Diameter (mm): 8
Thickness (mm): 6.2

Example 6

Global Compositions

Substance	mg/tablet (theoretical weight)
	0.3 mg
Moxonidine 1% in lactose	30.0
Glycerylbehenate (Compritol 888 ATO)	27.0
Lactose pulvis H_2O	79.76
Mg-stearate	3.0
Hydroxypropylmethylcellulose (Methocel E50)	-
Hydroxypropylmethylcellulose (Methocel K4M)	79.76
Hydroxypropylmethylcellulose (Methocel K100M)	60.0
Polyvinylpyrrolidone (Plasdone K29-32)	15.0
Colloidal Silicon Dioxide (Syloid 244)	2.0
Yellow ferric oxide	0.5

Total tablet weight: 297.02
Diameter (mm): 8
Thickness (mm): 6.2

Example 6

Barrier Blend

% w/w	STARTING MATERIALS
39.88	Hydroxypropylmethylcellulose (Methocel K4M Premium®)
39.88	Lactose Pulvis, H_2O
13.50	Glyceryl behenate (Compritol 888ATO®)
5.00	Polyvinylpyrrolidone (Plasdone K 29-32®)
0.25	Yellow Ferric Oxide
1.00	Mg Stearate
0.50	Colloidal Silicon Dioxide (Aerosil 200®)
100.00	

Example 6

Active Blend

mg/tab	STARTING MATERIALS
30.00	Moxonidine 1% in Lactose
60.00	Hydroxypropylmethylcellulose (Methocel K 100M Premium®)
5.00	Polyvinylpyrrolidone (Plasdone K 29-32®)
1.00	Mg Stearate
1.00	Colloidal Silicon Dioxide (Aerosil 200®)
97.00	

In-Vitro Drug release (Ph. Eur. 2nd Ed. V.5.4, apparatus 2, 500 ml water, 100 rpm, 37°C)

after 2h	23%
4h	39%
8h	65%
10h	77%
12h	86%
16h	96%

The formulations of Examples 4-1, 4-2, 5 and 6 were evaluated in a limited clinical trial.

The objectives of this study were (1) to provide data for the comparison of the bioavailability of four different controlled release formulations of moxonidine after single dose administrations and (2) to test the food effect for one of the formulations in five additional subjects. The formulations, three dosed as 0.3 mg tablets and one as 3 tablets with 0.1 mg each, were compared to a marketed immediate release reference formulation (Comparative Example B) containing 0.2 mg moxonidine per tablet.

Material and Methods

The formulations of Examples 4-1, 4-2 and 6 with 0.3 mg moxonidine per tablet and the formulation of Example 5 contained 0.1 mg moxonidine were used.

The study was conducted in an open, randomized, 7 day wash-out design consisting of 5 study periods with single dose administration after an overnight fast. The first four study periods were carried out in a four-way crossover design including the formulations of Comparative Example B, Example 6, Example 4-2 and Example 5. In the fifth period, the same subjects received the formulation of Example 4-1 as single dose administration. The study population consisted of 10 healthy fasted subjects of either sex. The formulation of Example 6 was also tested in a parallel group of 5 additional subjects who were dosed after the United States Food and Drug Administration (FDA) high fat breakfast.

During each study period, the subjects received a single oral dose with 240 ml of room temperature tap water. For quantitation of moxonidine, 15 blood samples were collected at different times before and up to 12 hours for Comparative Example B and up to 22 hours for the formulations of the present invention after the administration of the dose. Plasma concentrations of moxonidine were determined using a GC-MS method with a limit of quantitation (LOQ) of 0.025 ng/ml described below.

Aliquots of human plasma (1.0 ml) are fortified with 25.0 µl (10 pg/µl working internal solution) of internal standard (Clonidine.HCl). Each sample is extracted into ethyl acetate under basic conditions, the organic layer is removed, and the plasma discarded. Samples are back extracted with 0.5 M HCl and the organic layer is discarded. Samples are then exracted into methylene chloride under basic conditions, the aqueous layer is discarded and the organic layer is taken to dryness under a stream of nitrogen. The dried sample residues are derivatized with 3,5 bis(trifluoromethyl) benzoyl chloride and again evaporated to dryness under nitrogen. Samples are reconstituted in 50 µl of acetonitrile, transferred to plastic gas chromatography autosampler vials and injected (1 µl) onto the GC/MS system.

Experimental data of the formulations were normalized to 0.3 mg of moxonidine, according to the true content shown

in table 1; the true content of the reference is assumed to be equal to the nominal content, i.e. 0.2 mg.

Table 1. Nominal and true moxonidine content of the formulations. The true contents of the formulations were 94-109% of the nominal content.

Formulation	Nominal content (mg)	True content (mg)
Comparative Example B	0.200	0.200 assumed
Example 4-1	0.300	0.287
Example 6	0.300	0.282
Example 4-2	0.300	0.327
Example 5	0.300	0.300

The maximum plasma concentration (C_{max}) for each formulation was obtained from the content-adjusted data series. The area under the plasma concentration vs. time curve up to the last quantifiable concentration ($AUC_{0\text{-}tlast}$) was calculated using the linear trapezoidal rule. The apparent elimination rate constant (λ) was calculated by linear regression of the terminal segment of the log-linear transformed concentration vs. time curve and was used to extrapolate the AUC to infinity ($AUC_{0\text{-}\infty}$). The plateau time $t_{50\%Cmax}$ corresponds to the time span during which plasma concentrations are higher than 50% of C_{max}.

The relative bioavailability of each of the formulations of the present invention to Comparative Formulation B was calculated in the following two ways representing an upper ($F_{rel(1)}$) and a lower limit ($F_{rel(2)}$).

1. $F_{rel(1)} = AUC_{0\text{-}inf\ Example}/AUC_{0\text{-}inf\ comparative\ B}$

2. $F_{rel(2)} = [AUC_{0\text{-}tlast\ Example} + (C_{tlast\ Example}/\lambda_{comparative\ B})]/AUC_{0\text{-}inf\ Comparative\ Example\ B}$ where $AUC_{0\text{-}inf\ comparative\ Example\ B}$ was normalized to 0.3 mg to account for the dose differences.

Point estimates and 90% confidence intervals for the ratios of the means between the invention formulations were calculated based on the log-transformed C_{max} and $AUC_{0\text{-}tlast}$ values using pairwise ANOVA. Formulations of Example 6 and 5 are

judged to be bioequivalent when the 90% confidence interval for the ratios of the log-transformed data fall within 0.8 to 1.25.

Results and Discussion

Individual plasma concentration vs. time curves for the comparative formulation as well as curves for the invention formulations were prepared. The plasma concentrations for one subject (in the treatment with Example 4-2) showed at 6 and 12 h exceptionally high values with corresponding high impact on the PK parameters and the mean values. These two concentrations were excluded from the data set and from the PK analysis.

PK parameters are listed in tables 2 and 3. The PK parameters for Comparative Example B found in this study (*values given in parentheses*) were similar to those reported in the literature (1): C_{max} 1.29 $\pm$ 0.32 (2.14 $\pm$ 0.4) ng/ml, t_{max} 0.74 $\pm$ 0.35 (median 0.5) h, $AUC_{0\text{-}tlast}$ 4.1 $\pm$ 1.9 (5.8 $\pm$ 0.2) ng h/ml, and $t_{1/2}$ 2.12 $\pm$ 0.58 (2.06 $\pm$ 0.10) h. All invention formulations showed significantly lower C_{max} values than the immediate release formulation (C_{max} 3.2 $\pm$ 0.4 ng/ml dose normalized) and a greater prolongation of the plasma levels, consistent with their slower release in vitro. All invention formulations yielded very good relative bioavailability compared to the immediate release formulation.

The intrasubject variability seen for moxonidine in this study was generally lower for AUC than for C_{max}. Half of the subjects showed a relatively large variability in C_{max}. For AUC, one subject showed higher variability compared to the other subjects.

As the testing of the formulation of Example 6 in the fasted and in the fed state was performed in different subjects, the PK parameters are not directly comparable. However, they appeared to be in the same range with somewhat lower AUC values in the fed state.

The concentration-time profiles of the formulations of Example 6 (0.3 mg) and Example 5 (0.1 mg given in 3 tablets) appeared to be superimposable suggesting bioequivalence.

Table 2: *Summary of PK parameters for fasted treatments. "Mean" refers to geometric mean for C_{max} AUC and F_{rel}; median for t_{max} and $t_{50\% C_{max}}$. Sample size: 10.*

Parameter (unit)	Treatment	Mean	Coefficient of variation (%)	Minimum	Maximum
C_{max} ng/ml	Example B	2.14	40	0.96	3.46
	Example 4-1	0.69	24	0.44	0.95
	Example 6	0.57	21	0.42	0.81
	Example 4-2	0.54	20	0.38	0.83
	Example 5	0.54	14	0.46	0.72
t_{max} (h)	Example B	0.50		0.50	2.00
	Example 4-1	3.50		2.00	6.00
	Example 6	3.50		3.00	4.00
	Example 4-2	3.00		2.00	4.00
	Example 5	3.00		1.00	6.00
$AUC_{0-tlast}$ (ng/mlOh)	Example B	5.81	19	4.51	8.01
	Example 4-1	7.50	18	5.70	10.2
	Example 6	6.78	20	5.29	9.73
	Example 4-2	6.02	14	4.90	7.45
	Example 5	6.48	11	5.40	7.46
$AUC_{0-\infty}$ (ng/mlOh)	Example B	8.91	18	4.60	8.10
	Example 4-1	9.03	21	7.13	14.2
	Example 6	8.25	24	5.83	12.4
	Example 4-2	8.49	28	5.52	12.5
	Example 5	8.62	20	6.92	12.7
$t_{50\% Cmax}$ (h)	Example 4-1	9.0		5.0	11.0
	Example 6	12.0		6.0	15.5
	Example 4-2	7.0		3.0	15.5
	Example 5	10.5		5.0	15.0
$F_{rel(1)}$	Example 4-1	101	11	81	117
	Example 6	93	17	68	123
	Example 4-2	95	31	63	169
	Example 5	97	12	75	118
$F_{rel(2)}$	Example 4-1	89	12	70	110
	Example 6	80	14	66	102
	Example 4-2	73	18	57	99
	Example 5	77	12	63	89

Table 3: Summary of PK parameters for fed treatment. "Mean" refers to geometric mean for C_{max} and AUC; median for t_{max}. Sample size: 5.

Parameter (unit)	Treatment	Mean	Coefficient of variation (%)	Minimum	Maximum
C_{max} (ng/ml)	Example 6	0.61	24	0.48	0.86
t_{max} (h)	Example 6	4.00		2.00	6.00
$AUC_{0-tlast}$ (ng/ml○h)	Example 6	5.77	22	4.27	7.77
$AUC_{0-\infty}$ (ng/ml○h)	Example 6	6.63	17	5.45	7.9

All four formulations of moxonidine of the present invention that were tested versus the marketed immediate release reference formulation showed a plateau in the concentration versus time profiles after single dose administrations. All formulations of the present invention also achieved a reduction of the intersubject variability for C_{max} and very good relative bioavailability. Furthermore, exceptionally few adverse effects were observed with all formulations of the present invention.

No statistically significant differences were seen between the formulations of Example 6, containing 0.3 mg moxonidine and Example 5 given as 3 tablets with 0.1 mg each. The formulation of Example 4-1 showed higher plasma levels and faster absorption than the formulations of Examples 4-2 and 6 and resulting in higher relative bioavailability.

We Claim:

1. A method for treating congestive heart failure comprising administering to a mammal in need of such treatment, an effective dose of moxonidine, or a pharmaceutically acceptable salt thereof, in an oral or implant nonimmediate release formulation.

2. The method of Claim 1 wherein said formulation is a unit dose of from about 0.01 mg to about 3.0 mg of moxonidine, or a pharmaceutically acceptable salt thereof.

3. The method of Claim 2 wherein said nonimmediate release formulation is an oral dosage form.

4. The method of Claim 3 wherein said oral dosage form is a delayed release system or a sustained release system.

5. The method of Claim 4 wherein said oral dosage form is a sustained release system.

6. The method of Claim 5 wherein said sustained release system is a controlled release system or a prolonged release system.

7. The method of Claim 3 wherein said oral dosage form is a diffusional system or a dissolution system, or a combination thereof.

8. The method of Claim 7 wherein said oral dosage form is a diffusional system.

9. The method of Claim 8 wherein said diffusional system is a reservoir system or a matrix system.

10. An oral or implant pharmaceutical formulation comprising an effective dose of moxonidine, or a pharmaceutically acceptable salt thereof, in association with one or more carriers, diluents or excipients to afford nonimmediate release of said moxonidine.

11. The formulation of Claim 10 wherein said nonimmediate release formulation is an oral dosage form.

12. The formulation of Claim 11 wherein said formulation is a unit dose of from about 0.01 mg to about

3.0 mg of moxonidine or a pharmaceutically acceptable salt thereof.

13. The formulation of Claim 12 wherein said oral dosage form is a delayed release system or a sustained release system.

14. The formulation of Claim 13 wherein said oral dosage form is a sustained release system.

15. The formulation of Claim 14 wherein said sustained release system is a controlled release system or a prolonged release system.

16. The formulation of Claim 12 wherein said oral dosage form is a diffusional system or a dissolution system, or a combination thereof.

17. The formulation of Claim 16 wherein said oral dosage form is a diffusional system.

18. The formulation of Claim 17 wherein said diffusional system is a reservoir system or a matrix system.

19. The formulation of Claim 18 wherein said diffusional system is a matrix system.

20. The formulation of Claim 19 comprising, by weight, 0-40% lactose; 0-85% calcium phosphate; 9-65% hydroxypropylmethylcellulose; and 0.05-2.0% moxonidine, or a pharmaceutically acceptable salt thereof, and optionally containing one or more diluents, excipients, and carriers, provided that at least one of lactose and calcium phosphate is present.

21. The formulation of Claim 20 wherein said oral dosage form is a tablet comprising a core disposed within a barrier vehicle wherein

a) said core comprises, by weight, of the core:
9-40% lactose;
0-40% calcium phosphate;
9-65% hydroxypropylmethylcellulose;
2-8% polyvinylpyrrolidone;
0.1-2% magnesium stearate; and

0.05-2.0% moxonidine, or a pharmaceutically acceptable salt thereof; and

optionally containing one or more diluents, excipients and carriers; and

b) said barrier vehicle comprising, by weight of the barrier vehicle:
30-50% hydroxypropylmethylcellulose;
30-50% lactose;
2-8% polyvinylpyrrolidone;
0.1-2% magnesium stearate; and
0-0.1% moxonidine; and

optionally containing one or more diluents, excipients and carriers;

wherein said barrier vehicle partially covers the surface of said core.

22. An oral nonimmediate release formulation comprising moxonidine or a pharmaceutically acceptable salt thereof in association with one or more diluents, excipients and carriers to afford a mean plasma elimination half-life of from 6 to 16 hours.

23. The formulation of Claim 22 wherein said mean plasma elimination half-life is from 7 to 15 hours.

24. An oral nonimmediate release formulation comprising moxonidine or a pharmaceutically acceptable salt thereof in association with one or more diluents, excipients and carriers to afford a mean time to maximum plasma concentration of from 2.5 to 5 hours.

25. The formulation of Claim 24 wherein said mean time to maximum plasma concentration is from 2.5 to 4.0 hours.

26. A method of treating congestive heart failure comprising administering to a mammal in need of such treatment an effective dose of moxonidine or a pharmaceutically acceptable salt thereof, in an oral

nonimmediate release formulation affording a mean plasma elimination half-life of from 6 to 16 hours.

27. The method of Claim 26 wherein said mean plasma elimination half-life is from 7 to 15 hours.

28. A method of treating hypertension comprising administering to a mammal in need of such treatment an effective dose of moxonidine or a pharmaceutically acceptable salt thereof, in an oral nonimmediate release formulation affording a mean plasma elimination half-life of from 6 to 16 hours.

29. The method of Claim 28 wherein said mean plasma elimination half-life is from 7 to 15 hours.

30. A method of treating congestive heart failure comprising administering to a mammal in need of such treatment an effective dose of moxonidine or a pharmaceutically acceptable salt thereof in an oral nonimmediate release formulation affording a mean time to maximum plasma concentration of from 2.5 to 5 hours.

31. The method of Claim 30 wherein said mean time to maximum plasma concentration is from 2.5 to 4.0 hours.

32. A method of treating hypertension comprising administering to a mammal in need of such treatment an effective dose of moxonidine or a pharmaceutically acceptable salt thereof in an oral nonimmediate release formulation affording a mean time to maximum plasma concentration of from 2.5 to 5 hours.

33. The method of Claim 32 wherein said mean time to maximum plasma concentration is from 2.5 to 4.0 hours.

34. The use of 4-chloro-5-(imidazoline-2-yl(amino)-6-methoxy-2-methylpyrimidine, or a pharmaceutically acceptable salt thereof, in the preparation of an oral nonimmediate release medicament.

35. The use of claim 34, wherein said medicament is useful for treating congestive heart failure.

36. An oral or implant pharmaceutical formulation comprising an effective dose of moxonidine, or a

pharmaceutically acceptable salt thereof, in association with one or more carriers, diluents or excipients to afford nonimmediate release of said moxonidine.

37. The formulation of Claim 36 wherein said nonimmediate release formulation is an oral dosage form.

38. The formulation of Claim 37 wherein said formulation is a unit dose containing from about 0.01 mg to about 2.0 mg of moxonidine or a pharmaceutically acceptable salt thereof.

39. The formulation of Claim 38 wherein said oral dosage form is a delayed release system or a sustained release system.

40. The formulation of Claim 39 wherein said sustained release system is a controlled release system or a prolonged release system.

41. The formulation of Claim 38 wherein said oral dosage form is a diffusional system or a dissolution system, or a combination thereof.

42. The formulation of Claim 41 wherein said diffusional system is a reservoir system or a matrix system.

43. The formulation of Claim 42 comprising, by weight, 0-40% lactose; 0-85% calcium phosphate; 9-65% hydroxypropylmethylcellulose; and 0.05-2.0% moxonidine, and optionally containing one or more diluents, excipients, and carriers provided that at least one of lactose and calcium phosphate is present.

44. The formulation of Claim 43 wherein said oral dosage form is a tablet comprising a core disposed within a barrier vehicle wherein

a) said core comprises, by weight, of the core:

9-40% lactose;
0-40% calcium phosphate;
9-65% hydroxypropylmethylcellulose;
2-8% polyvinylpyrrolidone;
0.1-2% magnesium stearate; and
0.05-2.0% moxonidine; and

optionally containing one or more diluents, excipients and carriers; and

b) said barrier vehicle comprising, by weight of the barrier vehicle:
30-50% hydroxypropylmethylcellulose;
30-50% lactose;
2-8% polyvinylpyrrolidone;
0.1-2% magnesium stearate; and
0-0.1% moxonidine; and
optionally containing one or more diluents, excipients and carriers;

wherein said barrier vehicle partially covers the surface of said core.

45. A pharmaceutical formulation adapted for the treatment of congestive heart failure comprising as an active ingredient 4-chloro-5-(imidazoline-2-yl(amino)-6-methoxy-2-methylpyrimidine, or a pharmaceutically acceptable salt thereof.

46. An oral or implant pharmaceutical formulation comprising an effective dose of moxonidine, or a pharmaceutically acceptable salt thereof, in association with one or more carriers, diluents or excipients to afford nonimmediate release of said moxonidine.

47. The formulation of Claim 46 wherein said nonimmediate release formulation is an oral dosage form.

48. The formulation of Claim 47 wherein said formulation is a unit dose of from about 0.01 mg to about 2.0 mg of moxonidine or a pharmaceutically acceptable salt thereof.

49. The formulation of Claim 48 comprising, by weight, 0-40% lactose; 0-85% calcium phosphate; 9-65% hydroxypropylmethylcellulose; and 0.05-1.5% moxonidine, and optionally containing one or more diluents, excipients, and carriers provided that at least one of lactose and calcium phosphate is present.

50. The formulation of Claim 49 wherein said oral dosage form is a tablet comprising a core disposed within a barrier vehicle wherein

a) said core comprises, by weight, of the core:
   - 9-40% lactose;
   - 0-40% calcium phosphate;
   - 9-65% hydroxypropylmethylcellulose;
   - 2-8% polyvinylpyrrolidone;
   - 0.1-2% magnesium stearate; and
   - 0.05-2.0% moxonidine; and

   optionally containing one or more diluents, excipients and carriers; and

b) said barrier vehicle comprising, by weight of the barrier vehicle:
   - 30-50% hydroxypropylmethylcellulose;
   - 30-50% lactose;
   - 2-8% polyvinylpyrrolidone;
   - 0.1-2% magnesium stearate; and
   - 0-0.1% moxonidine; and

   optionally containing one or more diluents, excipients and carriers;

wherein said barrier vehicle partially covers the surface of said core.

51. A method for treating congestive heart failure comprising administering 4-chloro-5-(imidazoline-2-yl(amino)-6-methoxy-2-methylpyrimidine, or a pharmaceutically acceptable salt thereof, in an oral nonimmediate release formulation to an afflicted patient.

52. An oral or implant pharmaceutical formulation comprising an effective dose of moxonidine, or a pharmaceutically acceptable salt thereof, in association with one or more carriers, diluents or excipients to afford nonimmediate release of said moxonidine.

53. The formulation of Claim 52 wherein said nonimmediate release formulation is an oral dosage form.

54. The formulation of Claim 53 wherein said formulation is a unit dose containing from about 0.01 mg to about 3.0 mg of moxonidine or a pharmaceutically acceptable salt thereof.

55. The formulation of Claim 54 wherein said oral dosage form is a delayed release system or a sustained release system.

56. The formulation of Claim 55 wherein said oral dosage form is a sustained release system.

57. The formulation of Claim 56 wherein said oral dosage form is a diffusional system or a dissolution system, or a combination thereof.

58. The formulation of Claim 57 wherein said diffusional system is a reservoir system or a matrix system.

59. The formulation of Claim 58 comprising, by weight, 0-40% lactose; 0-85% calcium phosphate; 9-65% hydroxypropylmethylcellulose; and 0.05-2.0% moxonidine, and optionally containing one or more diluents, excipients, and carriers provided that at least one of lactose and calcium phosphate is present.

60. The formulation of Claim 59 wherein said oral dosage form is a tablet comprising a core disposed within a barrier vehicle wherein

a) said core comprises, by weight, of the core:

9-40% lactose;
0-40% calcium phosphate;
9-65% hydroxypropylmethylcellulose;
2-8% polyvinylpyrrolidone;
0.1-2% magnesium stearate; and
0.05-2.0% moxonidine; and

optionally containing one or more diluents, excipients and carriers; and

b) said barrier vehicle comprising, by weight of the barrier vehicle:
30-50% hydroxypropylmethylcellulose;
30-50% lactose;
2-8% polyvinylpyrrolidone;
0.1-2% magnesium stearate; and
0-0.1% moxonidine; and

optionally containing one or more diluents, excipients and carriers;

wherein said barrier vehicle partially covers the surface of said core.

INTERNATIONAL SEARCH REPORT

Int .tional Application No
PCT/US 97/09914

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/505 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 689 837 A (KALI-CHEMIE) 3 January 1996 see claims see examples ---	1-60
A	DE 43 25 491 A (BOEHRINGER-INGELHEIM) 2 February 1995 see the whole document ---	1-60
A	DE 39 04 795 A (BEIERSDORF) 23 August 1990 see claims see examples ---	1-60
A	EP 0 305 726 A (BEIERSDORF) 8 March 1989 see the whole document --- -/--	1-60

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
22 September 1997	30.09.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Scarponi, U

INTERNATIONAL SEARCH REPORT

Intu ional Application No
PCT/US 97/09914

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 246 549 A (BEIERSDORF) 25 November 1987 see the whole document ---	1-60
A	FR 2 441 625 A (BEIERSDORF) 13 June 1980 cited in the application see the whole document ---	1-60
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1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 1-9, 26-33, 51
is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. ional Application No
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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte. onal Application No
PCT/US 97/09914

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